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for doctors and their patients

Official Journal of the NORTH CAROLINA MEDICAL SOCIETY

January 1984, Volume 45, No. 1

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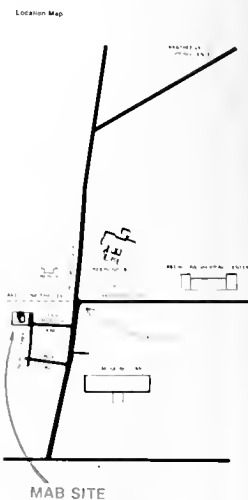
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Outpatient Adolescent Gynecologic Disorders

Joseph F. Russo, M.D.

THERE is increasing interest in the gynecologic disorders of adolescents. Early maturation and increased sexual activity have resulted in a need for medical consultation and treatment. One thousand sixty-four teenage females between the ages of 11 and 17 years made 3,540 visits to the Adolescent Gynecology Clinic of the UMD-New Jersey Medical School during a six-year period, one in 10 of the total gynecologic visits. The practitioner might then expect to see a young patient with a gynecologic problem approximately twice a day.

The types of gynecologic disorders with which adolescent patients presented on their visit were analyzed and grouped into broad categories. The goal was to document the relative frequency of various disorders. No attempt was made to detail the diagnostic and therapeutic methods employed since these have already been described.¹ The results highlight the gynecologic problems that are likely to be encountered in an office practice and point out the need for more attention to this specialized area of gynecologic care.

The seven types of gynecologic disorders in decreasing order of frequency were menstrual irregularities, genital tract infections, postabortion and postpartum referrals, lower abdominal pain, routine examinations, contraception, asymptomatic adnexal masses. The problems were similar to those of adult females. There was greater difficulty, however, in making a diagnosis and providing effective treatment. The approach of the physician and the staff to the adolescent female was different from that used with adult females because it took into account the young woman's stage of psychosocial development. No definitive diagnosis was made without a complete pelvic examination, which in some cases required a second visit. Pap smears were routinely performed. We convinced the patient of a need for a complete examination and performed it after receiving her consent.

Adolescence is a psychologic transition period between childhood and adulthood. This process does not depend on chronological age but is conditioned by pubertal growth and the societal environment. Three substages of psychosocial development during adolescence have been identified. Each affects and is affected by the adolescent's self-image and relationship with her family and her peer group.

During early adolescence the female understands little about how her body works, but is greatly concerned with her body image. It has been our experience that the early adolescent female usually comes with her mother and needs

her throughout the visit. Treatment and compliance depended on both.

At mid-adolescence most physical development is complete, but knowledge of bodily functions is often incomplete. Furthermore, the young woman's behavior is affected by the actions of her peers. Idealism and fantasy often dominate her thinking. The mid-adolescent female usually does not want her mother present during the medical interview and physical examination. Our approach has been to persuade the mother of her daughter's need to have a confidential relationship with her physician. Treatment and compliance depended on the young woman's understanding and willingness.

By late adolescence the young woman understands how her body works and is more realistic. Therefore, she is an easier patient with whom to deal and is not usually seen in our adolescent clinic.

One-fourth of the patients presented with a menstrual irregularity. The variations in adolescent bleeding pattern were many and it was difficult at times to identify the difference between physiologic normalcy and pathology. The practitioner must have a thorough understanding of the normal progression of physical changes associated with puberty. The diagnosis of constitutional amenorrhea, for example, was based on physical signs that the appropriate stage of pubertal development had not been reached. More than half of the young women were pregnant. The younger the teen, the less likely she or her mother were aware of this possibility. Therefore, patients were routinely screened for pregnancy prior to endocrinologic evaluation. Anovulatory cycles was another common cause for a menstrual disorder. The diagnosis can be established by observing the presence of normal secondary sexual characteristics, obtaining a normal serum prolactin, and inducing withdrawal bleeding with medroxyprogesterone. It has been our experience that the earlier the age of onset of menarche, the greater the interval between menarche and ovulation. Even though pregnancy and anovulation were the most common causes of menstrual irregularities, the practitioner must be prepared to exclude other causes. The routine use of oral contraceptives to regulate menstrual cycles prior to the establishment of a diagnosis should be avoided. A detailed discussion of the diagnostic and therapeutic approach has been described previously.²

One-fifth of the patients had a genital tract infection. Fortunately, 93 percent involved the lower genital tract only. Even though the majority of the patients with vaginal discharges were infected with either *Candida albicans* (38%) or *Trichomonas vaginalis* (32%), 9 percent were infected with *Neisseria gonorrhoeae*. Six percent of asymptomatic patients were infected with this microorgan-

From the Department of Obstetrics and Gynecology, East Carolina University School of Medicine, Greenville 27834.

ism as well. These findings support the need to screen all patients for its presence. During the course of pubertal development prior to the onset of menses, some teenage females in response to increased estrogen levels present with a profuse vaginal discharge containing desquamated vaginal cells.

Sixteen percent of the patients presented with lower abdominal pain. One-third had primary dysmenorrhea which could be relieved with either prostaglandin synthetase inhibitors or ovarian suppression with exogenous hormones. The others were difficult diagnostic problems. No cause could be found in 17 percent. Many patients had previously been told that they had chronic salpingitis, but only 14 had findings consistent with that diagnosis. A few patients had an ovarian cystectomy based on an ultrasonic diagnosis without cure of the pain. Since functional ovarian cysts are not uncommon in this age group, surgery should be deferred unless the cysts are large, persistent, or twisted. Laparoscopic evaluation is extremely helpful in establishing a cause in both acute and chronic pain.

A significant number of patients (20%) were healthy young women who were utilizing gynecologic services for the prevention of diseases or pregnancy. One hundred and ten patients requested routine examinations of the breast and pelvis or wished to be screened for venereal disease. In general, the visit was initiated by the mother of the young teenagers (11-14 years) or by the patient when older (15-17 years). Interestingly, all these patients had normal physical and laboratory findings. The majority of younger adolescents were not sexually active even though their mothers assumed that they were. It has been our impression that mothers were more likely to bring their young daughters to

be seen if they themselves had conceived during early adolescence. One hundred and nine patients came solely for contraception. The majority of these patients (90%) chose the oral contraceptives. Over 90 percent of the post-abortion and postpartum referrals left with a contraceptive method. Long term compliance (18 months), however, was poor (40%). Compliance could be improved if the mother of the younger teens were involved or with frequent office visits or phone contact with older teens. For patients seeking contraceptive advice, a specific approach was used.³

The impact of the increased level of sexual activity among adolescents on health care providers is evident from the data. Sixty percent of the patients came for their visit because they had a complication related to sexual activity (pregnancy, postpregnancy, infection, and contraception). These potential consequences of sexual activity should be explained to those young women who are considering becoming sexually active.

The data from this analysis point to the wide range of disorders that may affect adolescent females. In order to be effective the physician and staff must have an understanding of developmental psychology, physical growth and development, and gynecologic disorders. To this end, the author believes that the establishment of units for the specialized care of female adolescents with gynecologic disorders should be encouraged.

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Hypothalamic Releasing Factors for ACTH and Growth Hormone: Two Newly Discovered Peptides with a Promising Future in Clinical Medicine

David A. Ontjes, M.D., and Louis E. Underwood, M.D.

THE long-suspected connection between the brain and the endocrine system and the search for hypothalamic hormones was begun nearly forty years ago, when Geoffrey Harris of Cambridge University reviewed the available evidence and came to a compelling conclusion:

There is much experimental and clinical evidence that the hypothalamus is functionally linked with anterior pituitary activity. The most direct route by which this influence might be exerted is by means of the nerve fibers or blood vessels of the hypophyseal stalk. It seems possible to eliminate the nerve fibers from participation — however the portal vessels of the stalk, unlike the nerve fibers may undergo repair following stalk section, and so re-establish humoral transmission of stimuli.¹

Guided by the concept that humoral messengers might reach the pituitary via the hypophyseal portal vessels, investigators began the search for hypothalamic substances capable of causing the release of specific pituitary hormones. The isolation and elucidation of these releasing factors was hampered for many years by lack of precise and sensitive assays, and by the extremely small quantities of the factors actually present in hypothalamic tissue. The first major breakthrough occurred in 1970 when the laboratories of Guillemin and Schally first isolated and characterized the structure of thyrotropin-releasing hormone or TRH. One of the most exciting achievements in medicine in the past decade has been the elucidation of the structure and physiological characteristics of releasing or inhibiting factors for each of the classical hormones of the anterior pituitary. The names of the known factors and some of their major effects are summarized in table 1.

In this article we will review the current knowledge relating to the two most recently discovered factors, corticotropin-releasing factor, or CRF, and growth hormone-releasing factor, or GRF. Both have been isolated and characterized only within the past two years. Information on both is accumulating so rapidly that a lengthy review would be inappropriate and quickly out of date. We hope,

however, to provide readers with a short summary of important initial observations and a tentative assessment of the potential role of these hormones in clinical diagnosis and therapy.

Corticotropin-Releasing Factor (CRF)

More than 25 years ago, extracts of hypothalamus were found to stimulate ACTH release from pituitary tissues. Over the intervening years, a number of substances with corticotropin-releasing activity have been identified. Among these are vasopressin, norepinephrine, angiotensin II, and fragments of large proteins such as hemoglobin or myelin. None of these substances has met the criteria necessary to be considered a primary humoral regulator of ACTH secretion.^{2, 3} Interestingly, the substance now widely accepted as the physiological CRF was isolated as a by-product of a search for a quite different releasing factor.

Structure of Growth Hormone-Releasing Factor (GRF) Isolated from Human Pancreatic Tumor

H - Tyr - Ala - Asp - Ala - Ile - Phe - Tyr - Asa - Ser -
Tyr - Arg - Lys - Val - Leu - Gly - Gln - Leu - Ser - Ala -
Arg - Lys - Leu - Leu - Gln - Asp - Ile - Met - Ser - Arg -
Gln - Gln - Gly - Glu - Ser - Asn - Gln - Glu - Arg - Gly -
Ala - Arg - Ala - Arg - Leu - NH₂

Structure of Corticotropin Releasing Hormone Isolated from Sheep Hypothalamic Tissue

H - Ser - Gln - Glu - Pro - Pro - Ile - Ser - Leu - Asp -
Leu - Thr - Phe - His - Leu - Leu - Arg - Glu - Val - Leu -
Glu - Met - Thr - Lys - Ala - Asp - Gln - Leu - Ala - Gln -
Gln - Ala - His - Ser - Asn - Arg - Lys - Leu - Leu - Asp -
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Figure 1. Primary amino acid sequences of hpGRF-44 (from Esch, F. S., et al, reference 17) and ovine CRF (from Vale, W., et al, reference 3).

From the Departments of Medicine and Pediatrics, University of North Carolina School of Medicine, Chapel Hill 27514.

Table 1

Hypophysiotrophic Hormones Whose Structure Is Known

Hypophysiotrophic Hormone	Structure	Described Effects on Pituitary
Thyrotropin Releasing Hormone (TRH)	Tripeptide amide	Release of TSH, Prolactin
Gonadotropin Releasing Hormone (GnRH)	Decapeptide amide	Release of LH, FSH
Prolactin Inhibiting Factor (PIF)	Dopamine	Inhibition of Prolactin release
Corticotropin Releasing Factor (CRF)	Polypeptide amide (41 amino acids)	Release of ACTH, β -LPH, Endorphins
Growth Hormone Releasing Factor (GRF)	Polypeptide (approx 44 amino acids)	Release of Growth Hormone
Somatostatin or Growth Hormone Inhibiting Factor (SRIF)	Polypeptide (14 amino acids)	Inhibition of Growth Hormone release Inhibition of TRH-stimulated TSH release

Dr. Wylie Vale and his colleagues at the Salk Institute for Biological Studies began their purification of CRF with a side fraction of 490,000 fragments of sheep hypothalamus that had been processed earlier in a successful program to isolate gonadotropin-releasing hormone. The major fraction having CRF activity turned out to be a 41 amino acid peptide amide with the sequence shown in figure 1.³ The same laboratory quickly produced a facsimile of the native peptide using solid phase peptide synthesis, and developed a sensitive radio-immunoassay capable of measuring the peptide in biological materials. With an adequate supply of the synthetic peptide available for testing, the stage was set for rapid progress in characterizing the biological properties of this substance. Evidence to date strongly suggests that the peptide plays a central physiological role in controlling pituitary function.

Physiologic and Pharmacologic Effects of Ovine CRF. When tested for effects on rat pituitary tissues *in vitro*, synthetic ovine CRF releases equivalent quantities of both ACTH and β -endorphin or β -lipotropin. This is to be expected since both ACTH and β -endorphin are known to be products of a larger prohormone. Ovine CRF is at least 10 times more potent than any other substance known to have ACTH-releasing activity. Dose-related responses may be observed with *in vitro* concentrations of 10 pM or more,³ while preliminary estimates of immunoassayable CRF concentrations in rat hypophyseal portal blood are in the range of 100 pM or less.⁴ Human pituitary tissue responds to concentrations of ovine-CRF as low as 1 nM, suggesting that an identical or very similar peptide may be a physiologically significant CRF in man. Longer term exposure of adeno-hypophyseal cells to CRF leads to increased synthesis of ACTH as well as release.

The interaction of CRF with other factors that may also influence ACTH secretion is still in the early stages of investigation. Since an immediate effect of CRF on corticotropin-producing pituitary tumor cells *in vitro* is stimulation of cyclic AMP production, cyclic AMP has been proposed as a second messenger for the action of CRF, just as it has for many other peptide hormones.

Clearly, the negative feedback of glucocorticoids upon ACTH secretion will acquire new meaning when the interrelations with CRF are better understood. Thus far it is clear that glucocorticoids have a potent direct effect on the pituitary cell. Pretreatment of pituitary cells with very low (4 nM) concentrations of dexamethasone blocks the respon-

siveness of the cells to test doses of CRF in a non-competitive manner. The full blocking effect of the steroid requires 4 to 8 hours to develop and does not dissipate for up to 24 hours after steroid removal.⁵

It is quite likely that in addition to direct negative effects on pituitary cells, glucocorticoids will be shown to have a negative effect on the synthesis and secretion of CRF by the hypothalamus.² Immediately after bilateral adrenalectomy in rats, the content of immunoreactive CRF in the median eminence of the hypothalamus drops, suggesting depletion due to rapid secretion. However, after 2 weeks immunoreactive CRF levels in the same tissue rise to supernormal levels, as if a compensatory increase in the rate of CRF synthesis has occurred.⁶

CRF as a Diagnostic and Therapeutic Agent. One of the most frequent causes of spontaneous Cushing's syndrome is hypersecretion of ACTH by a pituitary tumor, most commonly a microadenoma. Since Cushing's syndrome may also be caused by hyperfunctioning primary adrenal tumors or by the secretion of excessive quantities of ACTH-like peptides by tumors of non-pituitary origin, accurate diagnosis of the etiology of cortisol excess is essential for appropriate treatment. The differential diagnosis of Cushing's syndrome has depended on the use of one or more of the tests summarized in table 2 and reviewed elsewhere.⁷ Generally, the most useful test in differentiating pituitary Cushing's disease from other causes of cortisol excess has been the so-called "low dose" dexamethasone suppression test, giving 2 mg of dexamethasone daily and measuring the effects on plasma cortisol and urinary 17-hydroxycorticosteroids. Early experience with CRF in patients with various forms of Cushing's syndrome suggests that the hormone may provide useful additional diagnostic information in some cases. Before the CRF test can be accurately evaluated, dosage regimens and normal ranges of response must be more accurately defined and standardized. It is clear at this time that both normal subjects and most subjects with pituitary ACTH excess respond to intravenous CRF with increases in plasma ACTH (peak 15-30 min) and cortisol (peak 45-60 min).⁸⁻¹¹ The majority of patients with ACTH-secreting pituitary adenomas show a larger than normal increment in plasma ACTH after iv doses of CRF ranging from 100 to 200 μ g. A significant minority of such patients, however, show responses no greater than normal.^{9, 11, 12} Very few patients with other causes of Cushing's syndrome have thus far been

Table 2

Typical Responses of Normal Subjects and Patients with Cushing's Syndrome in Response to Several Diagnostic Tests

	Dexamethasone 2 mg/day	Dexamethasone 8 mg/day	ACTH Infusion	Metyrapone	CRF Infusion
Normal Subjects					
Plasma cortisol	↓ (< 5 µg/dL)	↓ ↓	↑ (> 15 µg/dL)	→	↑ (~ 2 fold)
Urinary 17-OHCS	↓ (0-3 mg/day)	↓ ↓	↑ (2-4 fold)	↑ (2-4 fold)	↑
Plasma ACTH	↓	↓ ↓		↑	↑ (~ 2 fold)
Pituitary ACTH Excess					
Plasma cortisol	→	↓	↑ ↑	↑ ↑	↑ ↑ or ↑
Urinary 17-OHCS	→	↓	↑ ↑	↑ ↑	↑ ↑
Plasma ACTH	→ or ↓	↓		↑ ↑	↑ ↑ or ↑
Ectopic ACTH Syndrome					
Plasma cortisol	→	→	→	→	→
Urinary 17-OHCS	→	→	→	→	→
Plasma ACTH	→ (remains high)	→		→	→
Primary Adrenal Tumor					
Plasma cortisol	→	→	→ or ↑	→	→
Urinary 17-OHCS	→	→	→	→	→
Plasma ACTH	→ (remains low)	→		→	→

tested, but failure of ACTH or cortisol to rise after CRF has been reported in the ectopic ACTH syndrome,¹⁰ primary adrenal tumor,¹⁰ and bilateral micronodular adrenal hyperplasia.⁹

Very little experience has been reported in the use of CRF for delineating the cause of hypopituitarism. One patient with isolated ACTH deficiency but otherwise normal pituitary function failed to respond to CRF, while another with a known hypothalamic lesion showed a brisk ACTH response.⁹ These case reports suggest that CRF may be helpful in evaluating cases of secondary adrenal insufficiency.

Doses of CRF of 200 µg or more can cause distressing side effects such as hypotension, flushing, dyspnea, and even cardiac asystole.^{12, 13} These problems suggest that doses should be limited to 0.3 µg/kg or 100 µg where side effects are mild and uncommon.

There have been no reports in which CRF has been used therapeutically as a means of restoring adrenal function in patients with secondary adrenal insufficiency. Although CRF appears to have a much longer half-life than most of the other hypothalamic releasing factors when given to man,¹³ its use in place of cheaper and more easily administered adrenal glucocorticoids appears improbable in the near future. In this early stage of our knowledge, extrapituitary effects of potential therapeutic value cannot be ruled out.

Growth Hormone-Releasing Factor (GRF)

Because of its potential usefulness in the treatment of dwarfism due to growth hormone deficiency, the isolation of the hypothalamic factor that stimulates growth hormone (GH) secretion by the pituitary has been eagerly awaited. Attempts over the past 20 years to purify GRF from animal hypothalami, however, have been unsuccessful, primarily because of the minute quantities present. A long awaited breakthrough came in November 1982, when investigators at the University of Virginia reported the isolation of a peptide with GH releasing activity from a human pancreatic tumor.¹⁴ The patient, a 21-year-old woman, presented with

signs and symptoms of acromegaly. Her serum growth hormone levels were markedly elevated and her serum somatomedin-C, the GH dependent peptide that is believed to mediate the growth promoting actions of GH, was nearly 10 times normal. Since her sella turcica was enlarged, a pituitary GH-secreting tumor was suspected. Pituitary tissue removed by transsphenoidal surgery, however, revealed hyperplasia of the GH-secreting cells, rather than a discrete adenoma. Furthermore, the patient's acromegaly persisted after operation, and a search was made for an ectopic source of GRF. A CT scan of the abdomen showed a 5 cm tumor in the tail of the pancreas. Within hours following its removal there was a dramatic fall in serum GH concentrations. Cell culture medium in which pieces of the tumor were incubated caused the release of GH from cultured rat pituitary cells.

Within weeks following the report of this patient with apparent ectopic GRF secretion, the amino acid structure of the active peptide that had been purified from the patient's tumor was determined.¹⁵ This peptide, referred to as hpGRF because of its origin in the human pancreas, has 40 amino acid residues. Based on sequence homologies this GRF is closely related to the glucagon-secretin family of peptides derived from the gut. Several synthetic replicates of varying length from the N-terminus of hpGRF possess full biological activity, suggesting the biological function depends on the amino acids nearest the C-terminus of the molecule.

Concurrent with the studies outlined above, Sassolas and colleagues in Lyon, France obtained a large islet cell carcinoma from the pancreas of another patient with the clinical picture of acromegaly. Studies of this tumor done by Guillemin and his associates at the Salk Institute resulted in the isolation of the same 40 amino acid residue peptide. In addition, this tumor contained a 44 amino acid peptide with even greater *in vitro* GH-releasing activity than the 40 residue peptide,¹⁶ and a 37 residue peptide with somewhat less *in vitro* activity.¹⁷ Since all three peptides had identical sequences from their N-terminus, it was postulated that

hpGRF-40 and hpGRF-37 were biologically active fragments of hpGRF-44.¹⁸

Although not yet proven, there is increasing evidence that pancreatic GRF is structurally identical with hypothalamic GRF. The active material extracted from the two sources behaves identically on gel chromatography. Using antibodies raised against pancreatic tumor GRF, and immunohistochemical techniques, it has been possible to localize GRF in neuronal cell bodies in the hypothalamus of several species. The axons of these neurons project to the median eminence and end in contact with the portal vessels connecting the hypothalamus with the pituitary.¹⁹

Actions of GRF *In Vivo*. The first *in vivo* studies on the action of GRF were done in anesthetized rats. As little as 33 ng of GRF-44 administered intravenously caused a detectable increase in serum GH in less than 5 minutes.²⁰ Using an iv dose of 55 ng GRF, the serum GH rose from basal values of ≈ 200 ng/ml to 9000 ng/ml. Despite their difference in *in vitro* potency, GRF-44, GRF-40 and GRF-37 were equipotent *in vivo*.

Studies in rats were quickly followed by observations on GH release following iv GRF administration (1 μ g/kg) to healthy men.²¹ In these experiments, serum GH concentrations were increased within 5 minutes. Beginning at pre-injection levels of 2 ng/ml or less, GH levels peaked at 20.4 ± 6.5 ng/ml between 30 and 60 minutes. Serum levels of a variety of other hormones were unchanged by administration of GRF, attesting to its biological specificity.

GRF as a Diagnostic and Therapeutic Agent. Many patients who suffer from GH deficiency have primary lesions of the hypothalamic-GH regulatory centers, rather than destructive pituitary lesions. In these patients there is radiologic or pathologic evidence of lesions localized to the hypothalamus. In other patients with so-called idiopathic hypopituitarism, the most common form of GH deficiency in children, there is almost invariably a normal increase in serum TSH levels after the intravenous administration of thyrotropin-releasing hormone (TRH). This implies that at least for TSH secretion, the pituitary itself is intact. Therefore, it is not surprising that when GRF is administered to a variety of hypopituitary patients, some show an increase in serum GH.^{22, 23} Although studies are not yet sufficient to draw firm conclusions, it appears that measurement of the GH response to GRF will be useful in determining whether patients with impaired GH secretion have hypothalamic or pituitary lesions. In general, however, responses in all hypopituitary patients are much less pronounced than in normal subjects.

When GRF is given to patients with acromegaly, two types of serum GH responses may be observed.²⁴ One group of patients shows rises in GH similar to those of normal subjects. These patients also show at least a 20% decline in GH in response to glucose. The second group has supernormal rises in GH, and only a small decline or a paradoxical increase in GH after administration of glucose. It is possible therefore that an exaggerated response to GRF is indicative of more active disease.

Thus, GRF already shows promise as a diagnostic tool. It should prove useful in localizing the functional lesions causing GH deficiency, and perhaps in distinguishing different forms of acromegaly. To date, studies are so

preliminary that the eventual role of GRF as a diagnostic agent cannot be precisely defined.

The peptide also offers promise as a form of treatment for patients who have GH deficiency due to hypothalamic disease. It is theoretically possible that chronically administered GRF could normalize GH secretion in such patients, restoring growth. It is also possible that GRF could prove useful in increasing GH secretion in a variety of patients with catabolic disease states, thereby promoting nitrogen retention or wound healing.

Summary. Both CRF and GRF are invaluable probes for defining the mechanisms regulating the secretion of ACTH and GH. In addition, their use in patients with endocrine disorders promises to provide new means for precisely defining the nature of a variety of illnesses. Finally, each has therapeutic potential. The opportunity is at hand to perform the studies needed to bring CRF and GRF to their full potential in the care of patients.

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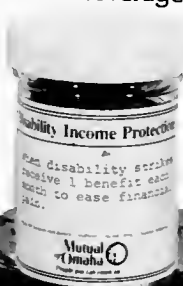
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An Uncommon Cause of Hematuria: The Patient's Story

Richard A. Davidson, M.D.

A 51-year-old counseling psychologist presented to North Carolina Memorial Hospital with the chief complaints of hematuria, decrease in exercise tolerance, generalized malaise, and recent onset of mild hypertension. The hematuria was first noted six months prior to his visit; it was initially noted as being just a mild discoloration of urine; microscopic evaluation at the health clinic which employed the patient revealed mild hematuria, which waxed and waned until he sought care. His systemic symptoms began around the same time; the patient jogged daily, and noted a definite change in his exercise capacity. One month prior to his visit he was found to be mildly hypertensive, with blood pressure measurements in the range of 140/95. Routine lab evaluation revealed a normal hematocrit and white blood cell count. The patient was seen by a urologist, who scheduled the patient for an IVP and cystoscopy. Prior to those procedures, he sought a second medical opinion. The patient lived in Chapel Hill, but questioning revealed that he and his wife had visited his son, who was in the Peace Corps in Swaziland, Africa, approximately 9 months prior to the onset of his symptoms. While in Africa, they had on one occasion gone swimming in a fresh water lake near their son's home. Twenty-four hour urine collections from the patient and his wife were evaluated by Dr. Norman Weatherly of the University of North Carolina School of Public Health and revealed the presence of eggs of *Schistosoma haematobium*. Both were treated with praziquantel in a dosage of 60 mg/kg/day, in three divided doses. Within 3 weeks, the patient noted a dramatic improvement in his systemic symptoms. Follow-up urine specimens were negative for parasites 2 months after treatment.

Discussion

In previous articles I have discussed case series of common human parasites seen at North Carolina Memorial Hospital. While these parasites represent the vast majority of cases diagnosed in our laboratory, more exotic parasites are occasionally seen; there have been four cases of schistosomiasis diagnosed at NCMH in the past four years.

There are four schistosomes that cause systemic infection in humans: *Schistosoma mansoni*, *Schistosoma japonicum*, *Schistosoma mekongi*, and *Schistosoma haematobium*. They are found in various parts of the world, including the Middle East, Africa, the Philippines, the Caribbean, Southeast Asia, Japan, and China. These parasites are blood flukes, and have an extremely complicated life cycle which includes an asexual stage in a specific aquatic snail as an intermediate host, and a sexual stage in humans. From the Division of General Medicine and Clinical Epidemiology, The University of North Carolina, Chapel Hill 27514.

the definitive host. All infections are transmitted through exposure to infected water, and the sexual forms that penetrate skin and cause the infection mature in the blood stream, mate in the liver, and live in venous plexuses; *S. mansoni*, *S. mekongi*, and *S. japonicum* live in the venous plexuses of the gut, and involve the portal circulation and the liver, causing hepatomegaly, portal hypertension and esophageal varices. *S. haematobium* lives in the venous plexuses of the bladder, causing hematuria, obstructive uropathy, and an increased risk of carcinoma of the bladder. Pathologically, the disease is an immunologic disorder in which the host response to the schistosome eggs causes fibrosis and granuloma formation.¹ The infection is chronic, and Pearson and Guerrant² estimate that 200 million people are infected worldwide, with 400,000 infected persons in the continental United States.

The diagnosis is made by finding the characteristic large eggs, with lateral or terminal spines depending on the species, in stool or urine. Patients may initially present with non-specific symptoms including fever and malaise; a travel history is essential in order to consider the diagnosis. Three stools will usually reveal the presence of gastrointestinal schistosomiasis; large amounts of urine should be concentrated to evaluate patients for *S. haematobium* infection.

Treatment of schistosomiasis has been extremely difficult in the past; the drugs which were most frequently used, metrifonate for *S. haematobium*, oxamniquine for *S. mansoni*, and antimony compounds for *S. japonicum*, are all toxic and have variable cure rates. A new drug, praziquantel (Biltricide; Miles Pharmaceuticals), is effective against all forms of *Schistosoma* species,^{2, 3} and is also effective against other trematodes and cestodes, including *Taenia* species, *Diphyllobothrium latum*, cerebral and visceral cysticercosis,⁴ and probably lung and liver flukes. The drug is usually given in three divided doses in one day for the treatment of schistosomiasis, but single treatments with as low as 5 mg/kg are effective against many cestodes. The drug may cause gastrointestinal upset, malaise or headache, but has not been found to have long-term toxicity. It is a welcome addition to the armamentarium of anthelmintic drugs.

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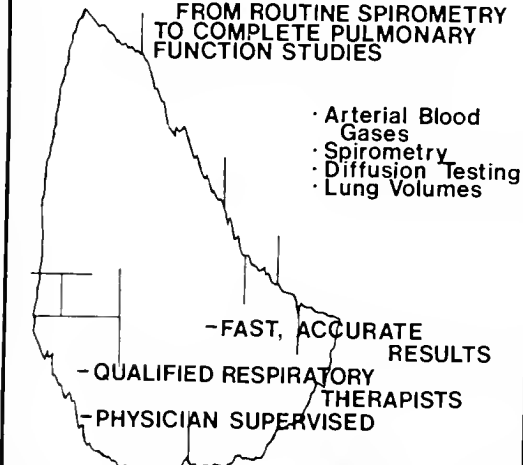
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BRIEF SUMMARY

PROCARDIA® (nifedipine) CAPSULES

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INDICATIONS AND USAGE: 1. **Vasospastic Angina:** PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation; 2) angina or coronary artery spasm provoked by ergonovine; or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina. Provided that the above criteria are satisfied, PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

2. **Chronic Stable Angina (Classical Effort-Associated Angina):** PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in those patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension may occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Excessive Hypotension: Although in most patients the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocker in patients who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone with low doses of fentanyl, or in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients usually receiving a beta blocker have developed heart failure after beginning PROCARDIA. Patients with aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug Interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in non-comparative clinical trials has shown that concomitant administration of PROCARDIA and beta blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antihypertensive effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, or discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Carcinogenesis, mutagenesis, impairment of fertility: When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose.

Pregnancy: Category C. Please see full prescribing information with reference to teratogenicity in rats, embryotoxicity in rats, mice and rabbits, and abnormalities in monkeys.

ADVERSE REACTIONS: The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients; transient hypotension in about 5%; palpitation in about 2%; and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antihypertensive medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, diarrhea, constipation, inflammation, joint stiffness, shakiness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, and sexual difficulties. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

Laboratory Tests: Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms. Cholestasis, possibly due to PROCARDIA therapy, has been reported twice in the extensive world literature.

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5%, palpitation in about 2% and syncope in about 0.5%)



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Arm Drift — A Frequent Occurrence in Normal Subjects

E. Wayne Massey, M.D., Barbara Scherokman, M.D., and Janice M. Massey, M.D.

ASSessment of arm "drift" (defined as any degree of arm "sag" or rotation (pronation) that could be observed during the set time period) is a part of the usual neurological examination. Distinct asymmetry of arm drift with arms extended at rest is usually noted in recording the neurologic examination, particularly when the history or examination is compatible with impairment of the lesser moved extremity. However, characteristics of arm drift among the normal population has not previously been studied formally.¹

Methods

An assessment of arm drift with the arm raised horizontally in front of the examinee was designed to duplicate conditions of the standard neurological examination. A total of 153 volunteers, 65 female and 88 male, ages 19-55, were asked to participate. The subjects with any history of prior neurological disorder were excluded. Sixty-five individuals underwent complete neurological examination by at least one examiner with normal results. Subjects with abnormal neurological examinations were excluded from the study. After observation and recording, each subject was then asked to complete a questionnaire which inquired as to his or her handedness, previous orthopaedic or head injury, surgery to either upper extremity, or history of meningitis or encephalitis. History of seizures, operation or illness excluded a subject from tabulation. No hospitalized or neurology clinic patients were included. No specific purpose of the study was disclosed to subjects.

The drift of each subject was assessed by one of three observers as would be done in the course of a neurological examination. Each fully clothed subject was asked to extend the arms horizontally in front of him with palms up, eyes closed and feet together. The elbows were fully extended, as were the wrists, and the hands were open with the palms up. Slow pronation of the wrist accompanied by slight flexion of the elbow and downward and lateral drift of the hand was defined as "arm drift" when observed.

TABLE 1

	Handedness	
	Right	Left
Right drift	91 (64%)	0
Left drift	8 (6%)	9 (75%)
No drift	42 (30%)	3 (25%)
Total	141	12

From the Division of Neurology, Duke University Medical Center, Durham (Drs. Massey) and Department of Neurology, Uniformed Services University of Health Sciences, Bethesda, MD (Dr. Scherokman).

They were observed for a period of 20-30 seconds on each occasion. The examination recorded only movements considered obviously asymmetric, although no attempt at quantitation was made. Examiners were unaware of the subject's hand preference.

Results

Twelve were left-handed. One hundred and forty-one were right-handed individuals. The assessment of each examiner was tabulated (table).

Among right handed subjects, 64% had a predominant drift on the right and 30% had no evident drift. The sample was not of sufficient size in left-handed individuals but none had more drift on the right in this small sample. Differences in right versus left were not influenced by age or sex of the subjects.

Comment

An attempt was made to duplicate procedures of the neurological examination. Therefore, although questioning the subject about handedness does not unequivocally establish cerebral dominance, the determination delineates this function as clearly as in routine clinical assessment. Routine neurological examination in 65 individuals supported their history of handedness.

The methods utilized obviously do not completely exclude neurological deficit in all participants. Sixty-five patients had a normal neurological examination. The sample was taken from a large, non-patient group, predominantly young adults who had no history of orthopaedic or major neurological disease. Grossly abnormal paresis, abnormal gait mechanisms, or hemisensory involvement seen in neurological disease were not encountered in any of the 95 subjects not examined.

Wartenberg¹ suggested that in many normal individuals some asymmetry of drift exists. Similarly, arm swing asymmetry may be present in normal individuals² and other asymmetries have been noted in neurological testing.³

It is apparent from our evaluation that an asymmetrical "drift" movement during neurological examination is not of itself an abnormal sign. To the contrary, bilateral equal movements are present in only a third of the group. A majority of healthy young adults who consider themselves right handed actually drifted their preferred right arm more than their left.

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The Identity and *in vitro* Antibiotic Sensitivity of Aerobic Gram-Negative Rods in a Community Hospital

Charles Ellenbogen, M.D. and Susan C. Hester, B.S., M.T.

THE best antimicrobial agent with which to treat an infection due to aerobic gram-negative rods (GNR) is one to which the causative microorganism is sensitive.¹ However, serious systemic infections due to GNR may require institution of antimicrobial therapy before the results of bacterial culture and sensitivity are completed by the microbiology laboratory and therefore before the prescribing physician can know the identity and antimicrobial sensitivity of the causative GNR. The physician's initial antimicrobial prescription in this setting can be made more rationally if the physician can accurately surmise the microorganism(s) that is most likely to be the cause of serious infection at a given anatomic site and the antimicrobial agent that is most likely to be effective against it.^{2, 3} Published reports of such data often originate from tertiary care medical centers.⁴⁻⁸ The identity and antibiotic sensitivity of microorganisms, especially GNR, which are most likely to cause infections in patients hospitalized in a tertiary care medical center, may not necessarily be the same as those causing infection in a community hospital.⁹ The purpose of this report is to present a limited description of GNR causing infections and their antimicrobial sensitivities in a community hospital in North Carolina.

Methods and Materials

Gram negative rods (GNR) isolated from clinical specimens were speciated using API (20E) strips. Isolates were stored on nutrient agar slants at 4 degrees C and tested for antimicrobial sensitivity in batches of 40.

Antimicrobial testing was performed according to the methods and standards of the National Committee for Clinical Laboratory Standards (NCCLS M2-825, Volume 2, Number 2, March 1982). Discs containing antimicrobial agents were purchased from Becton-Dickenson Company and stored in a desiccator at 4°C. Batches of organisms were tested with control organisms ATCC strain 29522 *E. coli* and ATCC strain 27853 *Pseudomonas aeruginosa*. For testing, organisms stored on nutrient agar slants were grown up on MacConkey agar. Three to five colonies were then picked using an inoculating loop, transferred to tryptic soy broth and incubated at 35°C for 24 hours until turbidity was equivalent to 0.5 barium sulfate. This suspension was used to inoculate a Mueller-Hinton agar plate as described

by NCCLS. Isolates were characterized as resistant, intermediate or sensitive using NCCLS standards.

Antimicrobial agents tested in our laboratory on routine clinical isolates of GNR include aminoglycosides (Gentamicin and Tobramycin), previously available penicillins (Ampicillin and Carbenicillin), and cephalosporins (Cephalothin and Cefamandole). Other agents are also routinely tested but are not reported because of the rarity of either their indication or their use as primary agents for the therapy of systemic infection caused by GNR: Kanamycin, Tetracycline, Chloramphenicol, Colistin, and Trimethoprim/Sulfamethoxazole. Separately tested were Amikacin, newer penicillins (Mezlocillin, Azlocillin and Piperacillin) and cephalosporins (Cefoxitin, Cefotaxime, Cefoperazone, and Moxalactam) and then only on isolates found to be multiply resistant upon routine testing or upon the request of the physician.

Testing for this study was rigorously controlled through both batch testing as described and simultaneous testing of all agents. Limitations in the time and manpower available to perform testing in this way limited the total number of isolates that could be tested to 200.

Results

Table 1 describes the GNR isolated according to the site from which the culture was obtained. Not described in table 1 are the two GNR isolated in blood cultures — *Klebsiella pneumoniae* and *Salmonella indiana*.

E. coli is the most common isolate, especially from urine and from wound and skin infections. *Pseudomonas aeruginosa* was the second most common and *Pseudomonas fluorescens* the fifth most common isolate jointly accounting for 16% of the total. These pseudomonads were especially important in nosocomial infections of the skin (including surgical wounds) and of the respiratory tract. *Proteus mirabilis* and *Klebsiella pneumoniae* were almost exclusively urinary pathogens and each accounted for less than 10% of the total. Other organisms were even less common with the exception of *Salmonella typhimurium* which was exclusively a stool isolate. The blood isolate of *Salmonella indiana* was not isolated from the patient's stool. The other less commonly isolated organisms were either predominantly urinary pathogens or demonstrated no specific site-pathogen association.

Table 2 contains the percentage of the five most fre-

From the Fayetteville Area Health Education Center and Cape Fear Valley Medical Center, Fayetteville 28306.

Table 1

Facultative (Aerobic) Gram Negative Rods Isolated on Culture by the Site of Origin of the Culture

	Urine	Wound/ Skin	Number of Isolates Sputum/ Respiratory	Stool	All Sites
Sample n:	146	21	16	11	200
<i>E. coli</i>	67	9	3	2	82
<i>Pseudomonas aeruginosa</i>	11	4	4	1	20
<i>Proteus mirabilis</i>	16	1	1	0	19
<i>Klebsiella pneumoniae</i>	13	0	2	1	17
<i>Pseudomonas fluorescens</i>	9	1	1	0	12
<i>Enterobacter aerogenes</i>	6	0	0	0	7
<i>Citrobacter freundii</i>	3	2	0	0	5
<i>Salmonella typhimurium</i>	0	0	0	5	5
<i>Enterobacter cloacae</i>	3	1	1	0	5
<i>Acinetobacter calcoaceticus</i>	4	0	1	0	5
<i>Serratia marcescens</i>	4	1	0	0	5
<i>Klebsiella oxytoca</i>	2	0	1	0	3
<i>Morganella morganii</i>	2	1	0	0	3
<i>Pseudomonas sp.</i>	2	1	0	0	3
<i>Serratia liquefaciens</i>	2	0	0	0	2
<i>Shigella sonnei</i>	0	0	0	1	1
<i>Salmonella indiana</i>	0	0	0	0	1
<i>Providencia stuartii</i>	1	0	0	0	1
<i>Proteus rettgeri</i>	1	0	0	0	1
<i>Klebsiella ozaenae</i>	0	0	1	0	1
<i>Proteus vulgaris</i>	0	0	0	1	1
<i>Pseudomonas cepacia</i>	0	0	1	0	1

quently isolated GNR that were susceptible to each drug. Some of the percentages have a superscript. The disc sensitivity method describes bacteria as either sensitive, resistant or intermediate. The intermediate level of sensitivity (to which the superscripts refer) is of marginal clinical value and is therefore reported separately.¹⁰

Aminoglycosides are the most uniformly effective antibiotics; however, Gentamicin and Tobramycin resistance is seen among pseudomonas isolates. Against these resistant isolates Amikacin, Cefoperazone and Piperacillin are the most efficacious (table 3). Against *E. coli*, *Klebsiella*

pneumoniae and *Proteus mirabilis* Cefamandole, Cefoxitin and to a lesser degree even Cephalothin are as effective as either Cefoperazone and Moxalactam or Piperacillin and Mezlocillin.

Many additional GNR were isolated in small numbers (table 1). When their antibiotic sensitivities (data not shown) are combined with those in table 2 a site-sensitivity association is derived (table 4). These data combined the frequency of isolation of the bacteria at each site (table 1) and their sensitivity (table 3) including the less common isolates.

Table 2

Antibiotic Disc Sensitivity to Most Common Facultative (Aerobic) Gram Negative Rods

	<i>E. coli</i>	<i>Klebsiella pneumoniae</i>	Percent Susceptible* <i>Proteus mirabilis</i>	<i>Pseudomonas aeruginosa</i>	<i>Pseudomonas fluorescens</i>
Sample n:	82	17	19	20	12
Amikacin	96%	100%	100%	100%	83%
Tobramycin	100%	100%	100%	75%	67%
Gentamicin	100%	94%	100%	70%	67%
Cefoperazone	94% ¹	88%	100%	90%	58%
Moxalactam	100%	88%	100%	30% ¹	33% ²
Mezlocillin	84%	88%	95%	75% ²	50% ³
Piperacillin	77% ²	82% ²	89% ²	95%	75%
Cefotaxime	98%	82% ³	100%	10% ^{2,3}	25% ³
Cefamandole	96%	94%	95%	0%	0%
Azlocillin	72% ²	35% ^{2,3}	95%	95%	75%
Cefoxitin	96%	88% ²	100%	0%	17%
Carbenicillin	72%	0%	100%	65% ²	58% ²
Keflin	73% ^{1,3}	94%	95%	0%	0%
Ampicillin	70%	0%	89% ²	0%	0%

* Fewer than 5% of isolates possess intermediate susceptibility except as follows:

¹ 5 to 9% of isolates possess intermediate susceptibility

² 10% to 12% of isolates possess intermediate susceptibility

³ 14% to 29% of isolates possess intermediate susceptibility

Table 3
Susceptibility of Gentamicin-Tobramycin-Resistant
Facultative (Aerobic) Gram Negative Rods to the Newer
Cephalosporins and Penicillins

	Number of 18 Isolates resistant to either Gentamicin or Tobramycin or both*		
	Sensitive	Resistant	Intermediate
Amikacin	14	3	1
Cefoperazone	14	2	2
Moxalactam	5	3	10
Mezlocillin	10	6	2
Piperacillin	13	5	0
Cefotaxime	4	7	7
Azlocillin	11	6	1
Carbenicillin	6	10	2

* 6 *Pseudomonas aeruginosa*; 4 *Pseudomonas fluorescens*; 3 *Pseudomonas* sp.; 1 each *Pseudomonas cepacia*; *Proteus rettgeri*; *Klebsiella pneumoniae*; *Serratia liquefaciens*; *Providencia stuartii*.

Table 5 describes the total cost per day to the patient receiving intravenous antibiotic therapy at the dosage and frequency recommended for the treatment of serious systemic infections.

Discussion

When a physician is caring for a patient whose clinical findings suggest a serious systemic infection due to GNR which requires immediate antibiotic therapy, one of the first steps is to collect and process those specimens of tissue or tissue fluid, such as blood, urine or cerebrospinal fluid, from which causative microorganisms can be cultured and sensitivity tests performed.^{1, 2} However, since it will be 24 or 48 hours before the initial results of these tests become available, the immediate selection of the initial antimicrobial agent must be made on other data. Such data as is reported here will permit the prescribing physician to sur-

Table 5
Cost of One Day of Intravenous Antibiotic Therapy

Drug	Dose	Interval Between Doses (hours)	Cost*
Amikacin	500 mg.	12	\$68.76
Gentamicin	80 mg.	8	\$69.54
Tobramycin	80 mg.	8	\$73.38
Cefazolin	1 gram	8	\$76.26
Moxalactam	2 grams	8	\$118.23
Cefoperazone	2 grams	8	\$124.68
Cefotaxime	2 grams	6†	\$144.72
Ampicillin	1 gram	4†	\$130.14
Cefamandole	1 gram	4†	\$149.70
Cefoxitin	1 gram	4†	\$163.26
Cephalothin	2 grams	4†	\$132.96
Piperacillin	3 grams	4†	\$167.88
Carbenicillin	3 grams	4†	\$158.34
Ticarcillin	3 grams	4†	\$165.06
Mezlocillin	4 grams	4†	\$200.40

* Includes direct cost of drug plus pharmacy admixture charge.

† Dosage for 70 kg adult with normal renal function and a clinical infection of moderate or intermediate severity or worse using Table 2 from *Annals of Internal Medicine* 1983;98:530-535.

mise the likely pathogens and to select the antibiotic(s) which is most likely to be effective. Moreover, combining these data with information about the cost of the alternative antimicrobial agents will permit the most cost effective initial antibiotic choice. Cost can be lowered by intramuscular as opposed to intravenous administration when appropriate as well as by use of a lower dose or less frequent dosing if clinical factors warrant.

There are many other factors that bear upon the selection of an antibiotic.^{3, 8} First, the physician must be aware that GNR are not the only possible pathogens for many infections and that antimicrobial agents effective against possible gram-positive pathogens and anaerobic gram-negative

Table 4
Antibiotic Disc Susceptibility of Facultative (Aerobic) Gram Negative Rods by Site of Origin of Culture

	Urine	Percent Susceptible			All Sites
		Wound/ Skin	Sputum/ Respiratory	Stool	
Sample n:	146	21	16	11	200
Amikacin	96%	95%	94%	100%	96%
Tobramycin	92%	86%	88%	100%	92%
Gentamicin	92%	86%	81%	100%	92%
Cefoperazone	96%	81%	88%	82%	85%
Moxalactam	85%	67%	56%	91%	80%
Mezlocillin	79%	81%	88%	91%	80%
Piperacillin	79%	86%	75%	82%	79%
Cefotaxime	79%	62%	56%	73%	75%
Cefamandole	74%	62%	50%	91%	72%
Azlocillin	70%	86%	63%	73%	71%
Cefoxitin	69%	43%	56%	91%	67%
Carbenicillin	63%	71%	56%	82%	64%
Keflin	56%	38%	31%	73%	54%
Ampicillin	42%	38%	6%	73%	41%

Fewer than 5% of isolates possess intermediate susceptibility except as follows:

¹ 5% to 9% of isolates possess intermediate susceptibility.

² 10% to 12% of isolates possess intermediate susceptibility.

³ 14% to 29% of isolates possess intermediate susceptibility.

⁴ 30% to 40% of isolates possess intermediate susceptibility.

⁵ 67% of isolates possess intermediate susceptibility.

pathogens must be added when clinically appropriate.² Some of the newer agents may be effective against both GNR and anaerobic gram-negative bacilli permitting the use of one drug instead of two (i.e., Cefoxitin or Cefotaxime instead of Clindamycin plus Gentamicin for peritonitis).^{11, 12} Second, the exact site of an infection and whether it is hospital or community acquired could be important.

For example, in our hospital a gram-negative pneumonia that is hospital acquired would likely have *Pseudomonas aeruginosa* or *Pseudomonas fluorescens* as the pathogen. This knowledge might prompt the prescriber selecting from among the newer agents to pick Piperacillin over Mezlocillin or Cefoperazone despite the apparent superiority of Cefoperazone or Mezlocillin overall against respiratory pathogens (table 4) because Piperacillin is the better anti-pseudomonas agent (table 2). However, Piperacillin and other anti-pseudomonal penicillins and cephalosporins should be prescribed with an aminoglycoside because of the danger of the development of resistance and subsequent clinical failure when used alone.¹²⁻¹⁴

Many host factors also bear upon antibiotic selection. Patients who have compromised immunologic function such as those who are neutropenic, or who have diseases such as sickle cell anemia or diabetes, or who have burns may require a different dosage, route or drug. Abnormalities of the function of the liver and of the kidneys bear upon the drug, dosage and route that ought to be selected.

Despite the limitations of the small number of observations reported here certain cautious conclusions seem permissible. Tobramycin and Gentamicin resistance was observed in 9% of isolates, especially pseudomonas, a rate higher than that found in another community hospital and similar to that found in some tertiary care medical centers.^{4, 9} Yet these aminoglycosides remain the most effective agents against non-pseudomonal isolates. Amikacin, Piperacillin and Azlocillin are the most effective anti-pseudomonal agents. The prescriber who wishes to avoid the use of an aminoglycoside would find that the most effective antibiotics are Cefamandole or one of the third generation cephalosporins for non-pseudomonas isolates.⁵

The cost of antibiotics can be substantial (table 5). The aminoglycosides appear to be the least costly agents in our hospital. However, the cost of one (\$76) or two (\$152) pairs of pre-dose and post-dose aminoglycoside serum

level determinations can increase the cost of 10 days of Gentamicin therapy (assuming no change in dosage or dosing frequency) from \$659 to \$811.

Cefamandole is less costly than either Cefotaxime or Moxalactam and may be, therefore, the beta-lactam of first choice for non-pseudomonas GNR infection. Piperacillin is the least costly anti-pseudomonal penicillin and considering its substantial overall effectiveness may be the most cost-effective beta-lactam to prescribe, keeping in mind the danger of using it alone mentioned above.¹⁵

In conclusion, knowing the identity and antimicrobial sensitivity of GNR by site of infection in patients at your hospital as compared with other hospitals may increase the accuracy with which you select the initial antimicrobial agent for treatment of a serious systemic infection.^{2, 16}

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Cryptococcal Arthritis of the Acromio-Clavicular Joint

Renee Adams and Malcolm McDonald

Cryptococcus neoformans is distributed worldwide; as a yeast it has the potential to cause life-threatening systemic disease in man. The primary clinical form of cryptococcosis usually affects the pulmonary parenchyma, presumably due to inhalation of organisms.¹ When hematogenous spread of the infection to extrapulmonary sites occurs, the most common metastatic foci are the central nervous system, kidneys, reticuloendothelial system, skin, and bone.² Joint involvement is rare. We could find only 11 cases of cryptococcal arthritis described in the medical literature.³⁻¹¹

Case Report

A 57-year-old black man was seen in March 1983 with a two-month history of increasing pain over the point of his left shoulder, associated with local swelling and tenderness. A radiograph done elsewhere ten days earlier had revealed a lytic lesion of the distal left clavicle, and fluid aspirated from the left acromio-clavicular joint showed a white blood cell count (WBC) of 217,000/mm³, with 90% neutrophils. No organisms were found on gram stain and culture on routine media.

The patient's past medical history was significant for pulmonary sarcoidosis diagnosed in 1946 by lymph node biopsy and originally treated with radiation. He required no further therapy until 1974, when worsening dyspnea necessitated treatment with prednisone 40 mg/day. From that time, the patient was maintained on corticosteroids in varying doses. During the 6 months prior to his March 1983 admission, he had received 10 to 15 mg of prednisone every other day, and his symptoms had remained stable.

The patient was employed as a nursing aide. He had no history of exposure to pigeons and denied recent increase in cough, sputum production, or headaches.

Upon admission the patient was afebrile, but tachypneic at rest. Auscultation of the chest revealed bibasilar rales and an expiratory wheeze. The left acromio-clavicular joint was swollen and tender, but without warmth or erythema. There was only slight limitation of shoulder movement. Neurologic examination was unremarkable.

A roentgenogram confirmed erosion of the left clavicle, with total obliteration of the acromio-clavicular joint, suggesting erosive arthritis. A radioisotope bone scan showed increased uptake at the left acromion and the distal clavicle.

Laboratory data on admission included a hematocrit reading of 47.7%, peripheral white blood cell count of

6,100/mm³, with no left shift, and a Westergren erythrocyte sedimentation rate of 3 mm/hr.

On April 8, 1983 the distal clavicle was resected and the fibrinous contents of the acromio-clavicular joint were removed. Histologic examination showed acute and chronic inflammation with histiocytes and giant cells. Fungal stains demonstrated budding yeasts with alcian blue-positive capsules. *Cryptococcus neoformans* was cultured from the surgical specimen. The organism was not recovered from cultures of blood or cerebrospinal fluid (CSF). Cryptococcal antigen could not be demonstrated by latex agglutination in samples of serum or CSF.

The patient was treated with a combination of amphotericin B and 5-fluorocytosine (5-FC). A total of 900 mg of amphotericin B was given over six weeks, together with 5-FC at a dose of one gram every six hours. He reported progressive decrease in left shoulder pain over the course of his therapy and was discharged pain-free in April 1983 to be followed in the Medical Outpatient Clinic.

Discussion

Cryptococcal arthritis was first described by Von Busse in 1894 when he made the observation in a case report that a "sarcomatous" lesion of the tibia had presumably eroded into the knee joint.⁴ Since that time very few cases of cryptococcal joint infection have been described; to our knowledge there are only eleven in the literature. The incidence of joint involvement is less than one would expect, since osteomyelitis due to hematogenous spread of cryptococcus occurs in approximately 10% of cases of systemic cryptococcosis.¹²

This case demonstrates several key points about cryptococcal arthritis. As in other cases reviewed, the disease was subacute in its presentation, with signs and symptoms of synovitis, but without further evidence of metastatic infection.¹³ Pulmonary symptomatology and an abnormal chest roentgenogram have been noted in half of the cases, although it is not always possible to distinguish between underlying pulmonary disease and pulmonary cryptococcosis. This is particularly true when the patient, as in this instance, has sarcoidosis. The association between cryptococcal osteomyelitis and sarcoidosis has been well described.¹⁴ Corticosteroid treatment of sarcoidosis is an additional aggravating factor. The conclusion drawn from previous reports that cryptococcal arthritis is secondary to adjacent bone infection agrees with the finding, in this case, of a lytic lesion in the distal clavicle in close proximity to the acromio-clavicular joint. This case demonstrates

From the Department of Medicine, Duke University Medical Center, Durham 27710.

an excellent response to a combination of amphotericin B and 5-FC, taking advantage of the reported synergistic effect of the two drugs,¹⁵ while reducing the amount of potential toxicity due to amphotericin B.

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The Durham Connection to Germany

Walter Kempner M.D.

Thoughts Upon Looking at the 1983 Commemorative Issue of the Postal Service of West Germany in Honor of The Hundredth Birthday of Otto Warburg, the Father of Cellular Physiology

“HERE in the Medical School of Heidelberg everybody wants to be a Professor and wants to teach and wants to talk. There was never anybody here who wanted to work. When something finally has to be done, they shout: ‘Mr. Ziegler, Mr. Ziegler!’ Doctor, I get sick to my stomach when I hear my name.”

Mr. Ziegler was the janitor who cleaned my glassware when I was an intern in Heidelberg where I did blood sugar determinations on dogs I had made diabetic by the injection of phlorizine. Mr. Ziegler had a fine upright character and I learned a lot from his pearls of wisdom, even when he was not completely sober and wore his hat on the back of his head while washing the pipettes and flasks.

I said, “Really, really, Mr. Ziegler, in all the time you were here wasn’t there ever anyone who did some work?” After a lot of deliberation he said, “Yes, several years ago there was one, but he left pretty soon and never became a Professor; and one never heard anything about him anymore.”

Sitting in the library a few days later, I looked to see if he had ever published a scientific paper and came across something about sea urchin eggs, nucleated red blood cells, and metabolic reactions of cancer cells. All of a sudden I found myself writing a letter to this unknown man whose address was in Dahlem, a suburb of Berlin, asking him whether I could work in his laboratory. He answered me politely that unfortunately he had only a very small laboratory where there was no space, but he would be glad to talk with me if I should come sometime to Berlin.

My ward consultant said that this was the most complete nonsense he had ever heard especially in my case since the big boss, Dr. von Krehl who had written the famous first book about pathological physiology (which incidentally was translated into English with an introduction by Osler), wanted to put me on the Staff as soon as I finished my internship. But I protested and said that I first wanted to learn something. My superior said, “It is much more important for your career to have been on the boss’s Staff a few years than to learn everything.” Anyway, I took the train to Berlin and Warburg talked with me in his small office. He was 43 years old, I was 24. He asked me, “Do you know any mathematics?” I said no. “Any physics?” I said no. “Any chemistry?” I said no. He said, “What actually do you know?” I said, “I graduated from the Medical School in Heidelberg and completed my internship there, and I published a paper about diabetes and did more

than 650 blood sugar determinations on a dozen dogs and a few rabbits. (The methods were not so simple then and I had to do all the determinations myself without the help of technicians.) So I really don’t know anything.” Warburg said, “At least you are honest. But you will see for yourself what I already wrote you that this is a very small laboratory and there is no space for anybody else. However, you can stay here for a couple of weeks and learn our methods.”

There were three young men without any previous training working there and three who had doctoral degrees. One was Dr. Wind who died of tuberculosis shortly afterwards; the second was Dr. Hans Gaffron, later well known for his work on photosynthesis, who was for many years Professor of Biochemistry at the University of Chicago; the third was Dr. Hans Adolf Krebs who became famous for his citric acid cycle and got the Nobel Prize a few years later. (Two other Nobel laureates had also started in Warburg’s laboratory: Otto Meyerhof and Hugo Theorell).

After the two weeks were over, Warburg asked me, “Did you learn our methods?” I said no. He asked “Why not?” I said I would need much more time to learn them. He asked, “How much time would you need?” I said, “Maybe one or two years.” “All right,” he said, “then stay here.” And I stayed there 1927 and 1928 in his small laboratory in the upper floor of the Kaiser Wilhelm Institute of Biology in Berlin-Dahlem and again in 1933 after an interval of five years in which I had been an Assistant Physician in the Medical School of Berlin.

In 1931 Warburg had got the Nobel Prize for his work on the respiration ferment and had been given a beautiful new institute of his own — the Kaiser Wilhelm Institute for Cellular Physiology in Dahlem.

Up until then he had published two books: *Metabolism of Tumors* (1926) and *Catalytic Effects of Living Substance* (1928). These books do not contain any opinions or discussions but are merely collections of the original papers he had written about the methods and results of his new experiments. One of his favorite remarks when he read the “literature” was, “There are two kinds of chemistry — experimental chemistry and paper chemistry.”

The titles of his later books (1948-1962) (also collections of original papers) are: *Heavy Metals as Active Groups of Enzymes*, *Hydrogen-Transferring Enzymes*, and *Further Developments in Methods of Cellular Physiology*.

In 1933, after Hitler came to power in Germany, a gentleman from the Rockefeller Foundation visited Warburg in his laboratory in order to persuade him to come to the United States. Warburg looked around and said, “Here

From the Department of Medicine, Duke University Medical Center, Durham 27710.

I know where each piece of apparatus is; here I can put my hand on everything I need," whereupon the visitor replied, "We will photograph the whole laboratory just as it stands down to the last detail. We will present you with an exact duplicate of your Institute." But Warburg couldn't make up his mind and remained in Germany throughout the rather unpleasant years before and during World War II.

Great scientists can be very average and boring people. Warburg was interesting. In 1927, my first year with him, I discussed in the evening with Dr. Krebs the results of an experiment I had just made that day. "There must be a mistake," Krebs said. I questioned why and he answered, "This is against all the laws of cellular physiology." The next morning when Warburg had come in, he asked me for the results of my experiment. I showed it to him and he said in English, "That's very exciting." I argued with my

newly acquired wisdom, "But it can't be true: this is against all the laws of cellular physiology." Warburg pondered a moment and then said, "Of course you have to repeat it six or seven times, but if it always comes out the same the laws of cellular physiology have to be changed."

In 1968, the year he became 85 years old, he sent me a letter for my 65th birthday and wrote, "In many respects I found that age is better than youth. The fight for existence is over and, if one possesses luck and reason, one can still live for many years. A bank account is desirable, a house of one's own is desirable, the possibility to do scientific work is desirable. I assume that you have all of this in ample measure. And so I dare to congratulate you."

"Luck and reason." But I think I would never have been lucky in any endeavor in medicine without those years 1927, 1928, and 1933 with Otto Warburg.

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Double, Triple, Toil and Trouble — Darvocet Intoxication

Ronald B. Mack, M.D.

WITH apologies to the Bard of Avon, this month's lesson will discuss *Darvocet* overdose. For those who do not already know, *Darvocet* is composed of *Darvon* (propoxyphene) and *acetaminophen*. In an overdose situation with this medication, we must deal with propoxyphene intoxication and acetaminophen intoxication and the problems created by their combination — hence the triple "toil and trouble."

Darvon — propoxyphene — is a centrally acting *synthetic narcotic* analgesic agent that is structurally similar to methadone except that it has relatively minor properties as a narcotic. There are currently two forms of this medication: (1) propoxyphene HCl, and (2) propoxyphene napsylate (*Darvon-N*). 100 mg of the napsylate has the equianalgesic effect of 65 mg of the HCl form. Over the years many questions have been raised concerning propoxyphene's efficacy as an analgesic. There is a fair amount of literature that suggests that *Darvon* is a weaker analgesic than codeine or even salicylates. It is stated that this drug is $\frac{1}{3}$ - $\frac{1}{2}$ as potent as codeine in relieving pain, that in doses less than 65 mg it is no more or less effective than a reasonable dose of aspirin. 200 mg of propoxyphene-N is felt to be better than placebo in ameliorating pain, however. In fact, *Darvon* is rather typically prescribed in combination with another analgesic such as aspirin or acetaminophen.

In spite of its less than ideal pain relieving attributes, *Darvon* products are very popular prescription drugs. However, propoxyphene is also a very common factor in drug associated deaths, the majority of which are suicides, and is probably only second to barbiturates in terms of its association with suicides and accidental death. It is also true that a very large proportion of propoxyphene related deaths appear to have occurred when this drug was ingested with ethanol and/or other CNS depressants. In addition to its acute overdose problems, *Darvon* has addictive potential, and physical dependence and narcotic withdrawal features occur with relatively chronic use, e.g., 600-800 mg daily over an 8 week period. A narcotic withdrawal syndrome can occur in neonates whose mothers are "users" of this drug. Dependence on this drug is not common, however, as the dose needed to produce physical dependence is associated with intolerable side effects. So far the drug is only available in oral form and is extremely damaging to veins if injected IV by the "serious" addict.

The adverse effects of propoxyphene include vertigo,

drowsiness, nausea and vomiting; less commonly, delusions, visual hallucinations, dysphonia, disorientation, abdominal pain and constipation can occur. (Nothing worse than being disoriented and constipated at the same time.) In *serious overdose*, however, propoxyphene produces the classic narcotic triad: (1) *coma*, (2) *respiratory depression* and (3) *miosis*. There are often some differences, however, between this classic triad and *Darvon* O.D. For example, *mydriasis* instead of *miosis* is not an uncommon event and *grand mal* or *focal seizures* are not unusual at all. The drug is rapidly absorbed and bound to tissues. Signs of overdose can occur as early as 30 minutes after ingestion and last easily 8-12 hours. As in other narcotic O.D.'s, non-cardiogenic pulmonary edema is a frequent visitor. A dose of 1-2 grams taken acutely by an adult can result in respiratory depression and seizures. Ingestions as little as 10.7 mg/kg have caused toxicity; at 35 mg/kg cardiorespiratory arrest has been reported.

The treatment of propoxyphene overdose involves: (1) gastric emptying, (2) activated charcoal, and (3) naloxone. The use of gastric emptying in propoxyphene overdose can be very tricky; because of the propensity for coma, seizures and respiratory depression soon after an overdose, very "cautious" gastric lavage would seem to be the wiser course. Activated charcoal works quite nicely here to bind the ingested propoxyphene remaining after gastric emptying. There are some good animal studies that suggest that repeated doses of activated charcoal could be quite beneficial in the treatment of this problem, i.e., repeated doses of 100-200 grams of activated charcoal, administered via N-G tube, in the first few hours post ingestion. In addition to providing respiratory support, the "big gun" used in the treatment of propoxyphene overdose is *naloxone* (Narcan), a very effective, safe, narcotic antagonist. The main objective of naloxone therapy is to produce a distribution of this antagonist sufficient enough to displace the intoxicating narcotic from its attachment to the narcotic receptor sites. Because naloxone is relatively safer, even in mega-doses, the recent recommendations concerning its use suggest increasing the dose. Therefore, for adults or children, administer initially 0.8 mg IV followed by 2.0 mg as needed. For those narcotics with longer half-lives ($T_{1/2}$), such as *Darvon*, one could consider using continuous IV infusion of naloxone, e.g., 4 mg/liter of naloxone at a rate of 400 μ g/hr (0.4 mg/hr) with less total fluids given (as indicated) to smaller children. Naloxone has a short $T_{1/2}$ of 30-60 minutes vs a $T_{1/2}$ of 12 hours for *Darvon*. Dialysis is ineffective because of the large volume of distribution of

propoxyphene. It is well to remember that one of the differences between propoxyphene and other opiate derivatives is the fact that propoxyphene can require much more naloxone to reverse the adverse effects. The seizures should be treated with naloxone initially. Serum and urine levels do not relate well to the amount of drug ingested or the degree of poisoning. Pharmaceutically speaking, the development and use of Darvon may not represent our finest hour.

Acetaminophen is the second part of this less-than-dynamic duo. This substance remains an ever increasingly popular OTC analgesic-antipyretic; new brands are still appearing of the drug alone, e.g., Panadol, and in a host of "cold remedies," "pain killers" (often associated with aspirin), "sinus medicines," etc. The addition of cyanide decreased the usage of at least one brand of acetaminophen for a while over a year ago, but now it seems that these non-aspirin products are being used more than ever. Although it was synthesized in 1877 and first used therapeutically in 1893, it wasn't until the 1950s that it was recognized as the active ingredient of phenacetin and not until 1955 that it was marketed as an OTC medication.

I like to use acetaminophen in children when I need to achieve some fever control and or pain relief and, in fact, I do not use salicylates in children unless they have a very select disease such as rheumatic fever, juvenile rheumatoid arthritis, Kawasaki's disease or osteoid osteoma. Acetaminophen is quite safe to use in children; unlike aspirin it does not undergo cumulative kinetics. That is, after a non-toxic dose of acetaminophen, the drug is completely metabolized and out of the body by 3 or 4 hours even if the patient is dehydrated and very febrile. It is not easy to cause a "therapeutic misadventure" with acetaminophen as it is in infants who are often given aspirin in too large a dose, in doses too close together, for too long a period of time. Acetaminophen can probably be given to children in much higher dosage than prescribed on the bottle. We give, when indicated, an initial dose of 20-25 mg/kg with subsequent doses of 15-20 mg/kg at 3-4 hour intervals. The toxic dose of acetaminophen in people over 9 or 10 years of age is about 140 mg/kg; the toxic dose in younger patients is not actually known at this time.

Acetaminophen overdose continues to be a big problem in at least two instances: (1) accidental ingestion by pre-school children, (2) purposeful ingestion by teenagers and young adults. If my recent experience is any indication, the problem of overdose with acetaminophen and acetaminophen-containing products is increasing. In order to understand the management of this overdose situation a bit of toxicokinetics must be discussed (I love that word!!). About 94% of ingested acetaminophen is conjugated in the liver with glucuronic acid and sulfate and excreted in the urine in a non-toxic form. About $4 \pm \%$ of the acetaminophen is metabolized in the liver, by the hepatic cytochrome P-450 mixed function oxidase system (say that 6 times rapidly!!) to an *active intermediate metabolite*. This metabolite is the bad news part of this whole mess; normally it is detoxified, in the liver, with glutathione and excreted in the urine. However, when 70% of the hepatic glutathione is used up (as in an overdose) this very active, obnoxious metabolite binds covalently to liver macromolecules and

causes acute centrilobular liver necrosis. A 70 kilo person who ingests 15.88 grams of acetaminophen acutely will probably use up 70% of hepatic glutathione and have liver injury as a result.

Without a good history, the diagnosis of acetaminophen toxicity is a very difficult one clinically and consists of about 3 phases. In the *first phase* which begins about 6 hours or more after ingestion of the overdose, there is nausea, vomiting, anorexia, diaphoresis, pallor and malaise (you know, I recently learned that not everyone feels like this on Monday morning) — all non-specific of course and not much help diagnostically. Phase I lasts about 12-24 hours. Coma or other evidence of CNS depression does not occur in this phase; if it does, you had better look for co-ingestants like ethanol, barbiturates, tranquilizers, sedatives or other CNS depressants such as our old friend propoxyphene. In this phase liver enzymes do not become abnormal. In *Phase II* the patients often say they feel better but in reality they are worse, i.e., the liver enzymes and serum bilirubin increase, the prothrombin time is prolonged, the liver is enlarged and tender. The majority of patients do not progress beyond this phase. (In acetaminophen overdose, hepatic toxicity is often defined as an SGOT of 1000 IU/L.) *Phase III* can be divided into two subgroups: (1) in the majority of patients there is a resolution of liver function abnormalities to a normal state. The peak of liver enzymes abnormalities is reached in about 72-96 hours and they resolve by 6-8 days; (2) in a very small number of overdose patients there is acute hepatic necrosis and liver failure complete with hepatic encephalopathy and death. Renal failure and cardiomyopathy can also occur. Be careful, renal failure may not be reflected by a rising BUN as urea production can be decreased secondary to hepatic necrosis. Patients surviving this toxic encounter experience no permanent liver sequelae.

The good news is that acetaminophen poisoning is quite treatable if you follow some basic principles such as: (1) *Empty* the stomach by conventional means depending on the consciousness of the patient. (2) *Do not give activated charcoal* if you have reasonable certainty that acetaminophen alone was ingested. The reason for this is really quite simple, i.e., the antidote for this poison is administered orally (at least it is in the United States) and the charcoal will absorb it. (3) Obtain an acetaminophen *blood level* at least 4 hours after ingestion, not before, and plot the result on the Rumack-Matthews acetaminophen overdose nomogram. (4) Obtain baseline lab studies such as CBC, platelets, prothrombin time, bilirubin, BUN, electrolytes, glucose and liver enzymes. (5) Give the antidote N-acetylcysteine (Mucomyst) if indicated. Now there is a catch to all of this — this antidote is not yet approved by the FDA even though it has been used for several years. Supervision for the antidote use can be obtained by calling the Rocky Mountain Poison Control in Denver, Colorado (toll-free 800-525-6115) where you will be entered on their protocol and given instructions.

You might ask if Mucomyst is the only treatment. Well, glutathione would be the perfect thing to use except you can't put it into the liver cells as yet. Methionine and cysteamine have been used but can have severe side effects. N-acetylcysteine which acts as a glutathione substitute

seems to have shown the greatest promise of preventing hepatotoxicity without significant side effects. In this county the antidote is given orally but in Great Britain it is administered intravenously. For the best results, N-acetylcysteine should be given in the first 16 hours post ingestion and becomes less effective as the 24th hour post ingestion is reached.

For reasons that remain unexplained even as we speak, acetaminophen toxicity is considerably less of a problem in preschool children. Very few cases of acetaminophen hepatotoxicity have been reported in this age group in this county. In our experience, at our hospital, we have not had a preschool child with an acetaminophen overdose who had an SGOT > 100. Nevertheless, be cool and use good clinical judgment when confronted with this poison in this age group.

I told you initially that there were three major problems in Darvocet overdose situations: (1) propoxyphene toxicity, (2) acetaminophen poisoning, (3) problems created by the combination of #1 and #2. It is to the latter problem that I wish to speak now. You see, I neglected to tell you that N-acetylcysteine is definitely "barf-city." This stuff smells so awful that when you walk into a room where it is being used and you are not aware of it, you walk gingerly so as to avoid stepping on something foul. It tastes about as bad as it smells and is classically given orally by admixture with Coca-Cola, Fresca, grapefruit juice, etc. in attempt to disguise the taste. It is quite irritating to the stomach with vomiting a likely result. If the patient vomits the oral dose within one hour of administration it needs to be repeated. But what would you do if the patient continues to vomit or is obtunded for any reason, but needs the drug? You would

insert a naso-duodenal tube of course. Aha, here is the rub and the point of this entire message. There was something else I didn't tell you; if the patient also ingested a narcotic-like substance along with the acetaminophen (like Darvocet) something confounding can happen to the GI tract. Opiates can remarkably decrease bowel motility to the point of ileus, can increase antral tone, can decrease the absorption of drugs taken orally and more importantly increase the tone of the first portion of the duodenum so remarkably that the passage of a tube into the duodenum may be difficult or impossible as long as 12 hours post ingestion. For this problem I would like to suggest a solution that I have not seen in print. If naloxone is as innocuous as we believe it is, why not give some in an attempt to reverse the spasm caused by the propoxyphene (or other opiates) so that the tube can be passed. It's worth a try!!

There are many important lessons to be learned here, but I believe that uppermost in the minds of those whose task it is to manage overdose patients is to remember that teenagers and young adults typically overdose in a polypharmaceutical fashion and you must look as hard as you can to determine what was consumed. For instance, if the clinical picture suggests a propoxyphene overdose, look for acetaminophen or aspirin overdose as well. If you fail to do this you might be treating one toxin only to have the patient die from another one.

As for me, no narcotics, thank you. I recently read where laughter can release your body's own endorphins and thus relieve pain. My latest research project involves the use of a large feather duster which I apply to the patient's bare feet postoperatively to see if I can relieve pain. The control group watches re-runs of "Leave It To Beaver."

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Features for Patients

Cut Off From People

LuVern H. Kunze, Ph.D.

Blindness cuts one off from things. Deafness cuts one off from people.

Helen Keller

Twenty million Americans or one of every ten people are "cut off from people" because their ability to communicate is defective in some way. Some, like Helen Keller, do not perceive what others are saying because of a decrease or absence of hearing. Others have adequate peripheral hearing but cannot understand what they hear because of deficiencies in the central nervous system. Still others lack the ability to express ideas and feelings through speech. The loss or reduction of the ability to communicate results in isolation and a reduced quality of life. The ability to learn is limited for lack of input of information. Opportunities for business and professional success are diminished. Interaction with family and friends is impoverished.

Communicative disabilities need not be accepted as inevitable and irreversible. Many communicative disorders can be treated effectively, particularly if they are identified early. Professionals who help the communicatively handicapped patient have methods for identifying such patients early.

Evaluation and treatment of hearing impaired persons is the responsibility of the audiologist. Evaluation and treatment of individuals having speech and/or language disorders is the responsibility of the speech-

language pathologist. To be licensed to practice in North Carolina, these professionals must have earned a masters degree and have completed a one year internship under the supervision of a licensed practicing professional. Nationally, speech-language pathologists and audiologists must meet the same requirements to obtain a Certificate of Clinical Competence from the American Speech-Language-Hearing Association.

There are many kinds of hearing, language, and speech disorders that may limit a person's ability to communicate with others.

Hearing Impairment

Children born with sensorineural hearing impairment are cut off from people more than any other group of communicatively handicapped persons. From birth, they are deprived of the sensory stimulation they need in order to acquire the language skills necessary for learning, communication with others, and economic success.

Early identification of children born with hearing impairment is essential if treatment is to result in the acquisition of acceptable language skills. Children learn to understand and use language in predictable steps with each skill acquired at a particular time during the first five years of life. Skills not acquired during this maximal learning period are learned with greater difficulty at later stages of development. The

longer the delay, the more difficult will be the learning process. The child whose hearing impairment is not identified until he is three years of age has lost the most important years of language learning.

Hearing impairment can be identified at birth through the use of auditory brainstem response (ABR) audiometry. This new technique measures electrical activity in the brainstem while sounds are being presented to the patient. A computer identifies both the extent of hearing loss and the location of the disorder causing the hearing loss. Because ABR audiometry does not require the cooperation of the patient, it is ideal for identification of the existence of a hearing impairment in infants, very young children and other hard-to-test individuals. Although complete description of the nature of the hearing loss must await the time when the child can cooperate in behavioral audiologic testing, vital treatment can begin as soon as the loss is identified. Hearing aid amplification and training for the best use of available hearing help the child acquire language skills during the normal learning period. Hearing status should be reevaluated regularly by the audiologist and the otologist to assure that amplification and medical treatment are appropriate. Counseling and training for parents help to assure normal social adjustment. As the hearing impaired child develops, special schooling may be required.

From the Division of Speech and Hearing Disorders, Box 3887, Duke University Medical Center, Durham 27710.

Illustrations by Ernest Croige, M.D.



If periods of hearing loss persist as the child enters school, poor academic performance may result.

The most common type of hearing impairment in preschool and primary aged children is the conductive hearing loss resulting from the accumulation of fluid in the middle ear because of otitis media (middle ear infections). Although such a loss is typically both mild and temporary, the child experiences significant difficulty in hearing and understanding what others are saying during periods of infection. It is important that medical treatment of otitis media take into account the impact of the hearing loss on the child's learning potential. Research has shown that frequently recurring ear infections during the language learning years can result in a significant delay in the acquisition of language and speech skills. If such periods of hearing loss persist as the child enters school, poor academic performance may result because verbally presented instructions and information are not understood.

Hearing impairment may be acquired at any age as the result of trauma or disease. Exposure to loud noise over a long period of time may produce significant hearing loss. In particular jeopardy are those close to loud music, noisy machinery or firearms without ear protection. Hearing loss resulting from noise trauma is irreversible, although it may be relieved partially by hearing aid amplification.

Reduction in hearing acuity is common among senior citizens. As hardening of the arteries progresses with age, the function of the cochlea (primary organ of hearing) is diminished because of the decrease in the blood supply to the area. Typically, such deficiencies produce both loss of sensitivity and reduction in discrimination skills. Although careful fitting of a hearing aid is likely to improve acuity, the patient may continue to experience difficulty in understanding what is being said, especially in a

noise-filled environment.

The task of the audiologist is to identify the hearing loss, to describe the degree of the loss at frequency levels important to understanding speech, and to provide information required to establish the cause of the loss. After medical treatment, the audiologist fits the patient with a hearing aid when appropriate and assists the patient to make maximal use of auditory and visual cues for communication.

Childhood Language Disorders

Many children are cut off from people because their abilities to understand and/or use language are defective, even though their hearing is normal. Such defects may be caused by a general delay in psycho-social development or may be specific to communication skills in a child who is developing normally in all other aspects.

Language is a complex system of

symbols used in listening, talking, reading and writing. Language development in the normal child begins with the acquisition of certain pre-language behaviors during infancy, progresses through a predictable sequence of acquired skills and is completed by the age of five years, except for the expansion of vocabulary that comes with increased education and experience.

Pre-language behaviors which must be learned before language can be acquired include looking into the face of a speaker (three months), turning toward the source of a human voice (four months), babbling and vocal play (four months), motor and vocal responsiveness to verbal stimulation by parents (five months), using short strings of consonant-vowel syllables (e.g., ba, doo, me) during vocal play (six months), stopping activity in response to "no" spoken sharply (six months), and imitating vocalizations of an adult with some accuracy (eight months).

A child's understanding of language used by others (receptive language) and his employment of language to express his desires, needs, ideas, and emotions (expressive language) develop in parallel, with receptive skills appearing a short time before comparable expressive skills. Acquisition of both receptive and expressive skills depends on innate potential for language learning and on stimulation and reinforcement by people in his environment.

After first words appear (10 to 18 months), the child's language skills increase rapidly in several areas, including development of ideas (concept formation); assignment of words to objects, actions, concepts, and emotions (semantics); acquisition of rules governing changes in words to designate tense, number, and case (morphology); learning rules governing word order and sentence structures (syntax); acquiring rules governing interpersonal communication (pragmatics); and perception and production of sounds and sound sequences for speech (phonology and

articulation).

Language learning is not a process of imitating what has been heard. It is a process in which a child develops rules about language that he then uses in generating sentences of his own. At first, his sentences are quite different from those used by adults. As he learns the rules, his sentences become like adult sentences.

Children have an inborn predisposition for learning language during the first five years of life. Potential for successful treatment of a language disorder is greater if it is identified early to take advantage of this period of heightened learning potential. Parents who are concerned that their child may be delayed in language acquisition frequently postpone seeking professional help, thinking the child might "outgrow it." Such a delay is very costly for the child who needs treatment, since his ability to compete in social and educational settings is limited by his inability to use language effectively. Such a delay is also unnecessary, since the speech-language pathologist is prepared to differentiate between those who will develop normally and those who will need treatment.

The speech-language pathologist has many tests and other evaluative procedures available to assist in describing the child's capabilities in each area of language utilization. A sample of the child's language is carefully analyzed to yield specific information about the ideas he is expressing, the words he is using, and the grammar he uses in forming sentences. Treatment plans are designed to improve the child's function in those areas in which performance is below the level expected of a child of his age.

The task of the speech-language pathologist is to structure learning experiences which help the child acquire rules that are consistent with acceptable adult language usage. Once these rules are learned, the child can generate sentences to express any idea he wishes and thereby

to participate fully in social and educational situations.

Aphasia

Aphasia is a language disorder that may be acquired at any age but is usually acquired in adulthood as the result of brain damage secondary to neurological disease (e.g., stroke) or trauma. Typically, there is a general reduction in language abilities across all language processes (understanding spoken language, reading, speaking, and writing), although the severity of the deficiency may vary from one language process to another.

The aphasic patient experiences a loss or reduction in available vocabulary. Words he hears no longer have distinct meaning. He has difficulty recalling words he needs for self expression. In general, words that are used most often are more likely to be retained or relearned. Words having closely associated meaning or words that sound alike are frequently confused. Word finding capabilities are decreased. The ability to attend to and retain verbal information is reduced or lost.

Reading and writing skills may be similarly lost or decreased. As visual perceptual skills are impaired, printed and written words lose their symbolic value and become meaningless marks on a page. The inability to conceptualize written symbols makes writing difficult or impossible. Visual field deficiencies may result in the patient's seeing only part of what appears in the visual field. He appears to ignore a part of the visual information available. The ability to attend to visual stimuli may be reduced. Deficiencies in the perception of spatial relationships create difficulty in following a printed line and in moving from line to line.

Articulation may be defective because the patient recalls imperfectly the motor movements and movement sequences required to pronounce words correctly. Speech sounds having similar motor movements may be substituted for one another.

Number concepts and computational abilities may be impaired.

Aphasia affects every part of the patient's life. The aphasic patient finds himself dependent on his family, friends, and other associates. He may lose control of many aspects of life, with decisions frequently being made for him. His effectiveness in business or professional life may be impaired, sometimes to the point that he must give up a position he has held for many years. His general effectiveness in human interaction is diminished or lost.

The responsibility of the speech-language pathologist is to describe through tests and observation the specifics of the patient's disorder and to plan a treatment program directed toward helping the patient communicate as effectively as possible considering his neurological state.

Voice Disorders

The sound that is used for speech is produced when air forced from the lungs vibrates the vocal folds (vocal cords). When the air supply is insufficient because of reduced lung capacity

or when the flow of air across the vocal folds is poorly controlled because of neurological impairment, voice production may be inadequate for intelligible speech production. Unpleasant voice quality or complete loss of voice may result when vocal folds are deformed, when the vocal folds are damaged by a blow, when polyps or nodules (abnormal growths) appear on the vocal folds because of vocal abuse, or when one or both of the vocal folds are paralyzed. Absence of voice results when the larynx containing the vocal folds is surgically removed because of cancer or other major trauma.

The speech-language pathologist participates with the physician in the description and diagnosis of voice disorders. Once medical treatment is complete, the speech-language pathologist may work with the patient to modify vocal production. When vocal sound production is no longer possible, the patient is taught to use alternative methods for sound production, using other organic structures (e.g., the esophagus), surgically created structures, or electronic devices.

Articulation Disorders

The sound produced by vocal fold vibration is modified by movements of the jaw, tongue, lips, and soft palate to produce the sounds of spoken language. Defective speech may result from improperly formed structures (e.g., cleft palate, short soft palate, malformed dental structure, etc.), deficient muscle control (e.g., cerebral palsy, etc.), or incorrectly learned articulatory movement.

Diagnosis of the articulation disorder is the responsibility of the speech-language pathologist. When the articulation disorder involves malformation of structures or deficient muscle control, further evaluation requires the expertise of the physician, the orthodontist and/or dental surgeon. With medical treatment complete, the speech-language pathologist undertakes retraining of the remaining articulation deficiencies, helping the individual obtain correct speech production on an habitual basis.

Fluency Disorders

Stuttering (dysfluency) is the fre-

Interaction with family and friends is impoverished.





In particular jeopardy are those close to noisy machinery without ear protection.

quent, apparently uncontrollable prolongation (audible or silent) of speech sounds and/or repetition of syllables, words, or phrases. The dysfluency may be accompanied by unusual movements of the speech mechanism or other parts of the body. The stutterer may report feeling tension, anxiety, fear of speaking or other negative emotions and/or sensations.

Although stuttering behaviors usually appear first in early childhood, not all children who are dysfluent during the early years of life (three to five years) will be stutterers. If a dysfluent speech pattern persists for six months, an evaluation should be sought with a speech-language pathologist to determine if the pattern observed is that expected of a stutterer or if it is a problem that should be self correcting.

The evaluation conducted by the speech-language pathologist provides a profile of dysfluent and associated behaviors which will be replaced with fluent behaviors during treatment.

Available Services

The goal of treatment of those who are cut off from people because of disorders of hearing, language, and speech is to help the patient acquire the best communication system permitted by his physical capabilities. When the disorder has no organic basis, the results of treatment may be normal communicative function. When the disorder is the consequence of some organic problem, the treatment goal is more effective communication even though completely normal function is not possible.

Diagnostic and treatment services by speech-language pathologists and audiologists are available from private practitioners and through many public and private agencies. Services for school age children are available in most public and some private schools. Services for people of all ages are available in most large hospitals and medical centers. Some public health agencies offer speech-language pathology and audiology services. Some cities have speech and

hearing centers separate from other institutions. People living in or near cities having major colleges or universities may be able to obtain services through professional educational programs. There are audiologists and speech-language pathologists in private practice in most cities.

Readers wishing to know if a particular practitioner is licensed in North Carolina may write the Board of Examiners for Speech-Language Pathologists and Audiologists, P.O. Box 5545, Greensboro, North Carolina 27403 or call 919/272-1828. To determine if a clinician holds the Certificate of Clinical Competence, write ASHA, 10801 Rockville Pike, Rockville, Maryland 20852 or call 301/897-5700. Individuals wanting information concerning speech-language pathologists or audiologists practicing in a geographic area may contact either of the above resources or the North Carolina Speech, Hearing and Language Association, 1821 Chapel Hill Road, Durham, North Carolina 27707 or call 919/493-3451.

The signals may be subtle. The disease is often fatal.

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There's A Fungus Among Us

Claude S. Burton, M.D., Peter Heald, M.D., and J. Lamar Callaway, M.D.

Man harbors so many microorganisms that the division between infection and harmless colonization is often obscure. There are in fact many microorganisms that are actually beneficial. Very little is known about the ecology of these organisms. The factors that make the difference between colonization and infection are obscure, though the immune response of the host and the local environment (temperature, moisture, and elimination of competing bacteria with antibiotics) is thought to be involved. Fungi are commonly found on surfaces of the human body yet rarely cause symptoms. It is to the organisms' advantage to reside in harmony with the host. If the organism troubles the host, then the host will take steps to eliminate the organism.

The dermatophytes are a group of fungi that have adapted themselves to man. Fifty percent or more of the adults of our species are found to harbor these fungi yet only a minority will ever have cause to see a physician or turn to over-the-counter medication for relief. However, that minority of Americans alone will spend over \$40,000,000 this year to treat fungal dermatitis.

In general, these fungi live in the most superficial layer of skin, the stratum corneum. This, the so-called horny layer, is composed largely of

keratin as are the hair and nails. Keratin, a durable fibrous protein that provides a barrier against the environment, is also the diet of the dermatophytes.

Only when growth of these fungi alerts the host's immune system are symptoms likely to occur. Once the immune system is alerted, an allergic reaction to the fungi develops along with signs and symptoms of what we know as fungal dermatitis. Fungal dermatitis is characterized by itchy, scaly skin, often with redness and swelling. Fungal dermatitis of the body is commonly referred to as ringworm or *tinea corporis* (the latter is the Latin terminology; the Greeks called this herpes). Fungal dermatitis of the foot is known as athlete's foot or *tinea pedis*. As one can see the nomenclature is geographic — referring to the part of the body involved.

Fungal dermatitis requires a multifaceted treatment. Key ingredients of a successful strategy include the following: antifungal chemotherapy, treatment of the allergic reaction, and modification of the environment that favors dermatophyte infection. Effective antifungal creams such as miconazole are useful topically and have the advantage of eliminating yeast, another cause of dermatitis that is often confused with fungal dermatitis. Systemic therapy with such agents may be required, especially if elimination of nail disease is

desired. When the allergic symptoms such as itch and swelling predominate, corticosteroids are a useful adjunctive therapy. Control of moisture on the feet (frequent sock and shoe changes, ventilated footwear, dusting powder) and in the groin area (loose clothing, dusting powder) are essential for the treatment of dermatitis in these areas. Despite the best of therapies, relapse is frequent. Like the mistletoe that finds the oak, the dermatophyte will find those with the right sort of "bark."

Finally, of prime importance is an accurate diagnosis. It cannot be over-emphasized that fungal dermatitis is often misdiagnosed and therefore mistreated. Acknowledging the propensity for fungal dermatitis to masquerade as other varieties of dermatitis, Dr. Callaway has established the dictum, "If it scales, scrape it." By demonstrating the fungus in scrapings of skin obtained easily and painlessly from suspicious rashes one can be certain of the diagnosis. And not all that looks like fungal dermatitis is actually due to fungi. We frequently see patients who have been told they have "ringworm" who actually prove to have psoriasis, sarcoidosis, or any of a dozen other conditions (including cancer) that require specific therapy. When a "ringworm" does not respond to therapy, seek professional advice.



IT'S GETTING TOUGHER FOR NANCY RAY TO BE A MOTHER.

Nancy Ray has multiple sclerosis.

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JUST WHEN YOU'RE STARTING TO LIVE, MS CAN STRIKE

EDITORIAL

Impact of Pregnancy on Adolescent Physical, Psychosocial and Socioeconomic Development

Joseph F. Russo, M.D.

THERE are approximately 21 million teenagers in the United States. An estimated 12 million are sexually active. Over one million become pregnant and 600,000 give birth each year. These births account for one-fifth of the total births in the United States.

Five percent of North Carolina's teenagers become pregnant each year of whom more than 24,000 are between 15 and 19 years of age and more than 750 are younger than 15 years. Fifteen percent of these teenagers are pregnant again within one year.

Adolescence is a unique time of physical and psychological growth and development. Since the onset of menarche does not signify the cessation of physical growth and pregnancy increases nutrient needs, we might well expect medical complications to be greater for pregnant adolescents. Since adolescence is a time of emotional growth, the teenager may not be emotionally capable of coping with the many stresses that accompany pregnancy and parenthood. Furthermore, health care providers uniformly feel inadequate when trying to provide services because teenagers are often noncommunicative and noncompliant.

Physical Impact

The obstetrical complications reported most often are maternal mortality, preeclamptic toxemia, anemia, prematurity, low birth weight newborn, and perinatal death. Older adolescents (16-19 years) who receive adequate prenatal care do not experience more obstetrical complications than adult women of the same race, parity, socioeconomic, and marital status.¹ The health of young women prior to conception and the quality of prenatal care during pregnancy influence outcome more significantly than does their age at the time of conception. There is growing concern, however, for the obstetrical outcomes of very young teenagers.

Young age can be a negative factor in regard to the physical readiness for pregnancy. If young women become pregnant before the cessation of their own growth, a dual growth demand is created. Early maturing females (menarche 11.6 years) grow more and for a longer period of time than late maturers (15.2 years) and are at higher risk for poor pregnancy outcomes.² Furthermore, the nutritional

status and dietary intake of pregnant teenagers are generally poor. About one-half have good diets, one-quarter have fair diets, and the remaining one-quarter have poor diets with deficient intake of calcium, ascorbic acid, vitamin A, protein and iron, and high intake of snack foods and soft drinks. The poorer the patient, the more deficient the diet. The nutritional status of the pregnant teenagers prior to conception and their diet during pregnancy are important determinants of their reproductive performance.³

Psychosocial Impact

Adolescence is a time when females develop psychologically as well as physically. Three substages of psychosocial development have been identified — early, middle, and late adolescence.⁴ Each substage has specific challenges that need to be negotiated in order to proceed to the next.

Early adolescent females experience the onslaught of puberty with all of the accompanying physiologic, endocrinologic and emotional changes. They are preoccupied with rapid body development and begin to self-explore. Involvement with girlfriends increases, which helps to loosen ties with mother and allows comparison of selves with peers. Dating is limited and usually in groups. The major challenge is the feeling of ambivalence between the emerging need for independence and the lingering need to remain close to mother. If they become pregnant, they usually know little, claim not to have been intimate with the boy, and deny that they are pregnant.

Middle adolescents are the stereotype of self-involved females. They actively seek autonomy from their families. Emotions swing wildly. Peers replace parents. It is a time of promiscuous heterosexual dating. The major challenge is the development of an identity separate from their parents. If pregnancy occurs, it is usually a result of experimentation, romantic fantasizing, or a need to have something of their own rather than as a consequence of intimate feelings toward the boy.

Late adolescents become involved in the resolution of love and work identity commitments. A more stable personality is formed and reality testing is greatly enhanced. They are comfortable with autonomy from their families. Love relationships are more intimate. Future goals and plans are formed. If pregnancy occurs, it is generally a result of needing to strengthen the intimacy they feel for the boy.

From the Department of Obstetrics and Gynecology, East Carolina University School of Medicine, Greenville 27834.

Therefore, the emotional transition from child to adult involves successfully resolving the conflicts arising from dependency versus independency needs and from the establishment of love and work identities. This transition is very stressful. If adolescent females become pregnant, additional challenges are added. They must now develop their role as future mothers and must make adjustments to the physical and emotional changes that accompany pregnancy. If pregnant teens are young, living at home and attending school, they must face parental disappointment and disruption of their families. Often decisions are made for them without consulting them. Therefore, pregnancy at a young age leads to conflict and confusion. It is likely to disrupt the normal process of psychosocial development.

Socioeconomic Impact

Pregnancy is the most often cited cause for young women to discontinue their educations. Mothers who give birth before they are 18 are only half as likely to graduate from high school as those who postpone childbearing until after they turn 20. The impact of pregnancy on education is not simply the result of poverty, low aptitude or lack of interest in learning. The majority of school systems do not deal with the problem of pregnancy in that they either excuse or exclude the young woman by providing home instruction or night school classes. In contrast, young pregnant women in a special educational facility complete school and the majority maintain or improve their grades. The number of years in school has a significant effect upon labor force participation and wage rate. Job experience is not an adequate substitute. Therefore, the fewer are the number of years in school the lower is the wage, and the less likely an individual will be motivated to find work.

The younger the woman at the time of delivery the greater the incidence of poverty and welfare dependency. Among women who deliver a first child at ages 13-15, 16-17, or 18-19 years, there is a 2.6, 2.0, or 1.4 times greater incidence of poverty, respectively, than among those who deliver their first baby after 20 years of age. The

mean family income of 1975 of white women who gave birth at 16 or younger was \$7,550, which is half the \$13,900 earned by families where the mother delayed giving birth until her twenties. The risk of separation and divorce rises as the age of parenting falls. Women who give birth at ages 14-17 are separated or divorced within 15 years at a rate three times the proportion among women who do not begin childbearing until age 20. Furthermore, younger mothers have larger families (50% more children) than do their older counterparts. In 1975, \$4.7 billion in Aid to Families with Dependent Children payments to families were made to mothers who gave birth in their teens. Early childbearing results in educational and economic deprivation as well as detrimental sociologic patterns of living. These effects are often perpetuated from one generation to the next.⁵

Many of these detrimental effects of early childbearing can be minimized. Successful programs use an interdisciplinary approach which includes a broad range of personal and health care services. All comprehensive care programs share common service components: communication between community, schools, and health care providers; early diagnosis and referral; continuity of care before, during, and after delivery; ongoing health care education with emphasis on reproduction, contraception, and newborn care; continuous classroom education; and routine inclusion of nutritional and psychological counseling and social work services as part of obstetrical care.

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"Hello, Pituitary? — Hypothalamus Calling!"

Francis A. Neelon, M.D.

ONS ago, soon after the first primitive Metazoa began their life on earth as multicellular organisms, the need for intercellular communication must have provided an irresistible stimulus to the evolution of appropriate communication systems. How else could any hungry hydra hunt, without a nerve net to coordinate the recognition and entrapment of its prey? Or the simple slime mold slither to fruition without a hormonal trumpet-call to organize the gathering of individual cells? Today we recognize that evolutionary development has continued along those two main paths, providing animals and man with both a nervous system for highly specific, point-to-point communication and an hormonal system for more diffused and generalized information transfer. Since the common purpose of these systems is to foster cooperation among the components of the organism, it is not too surprising that they should, in turn, interact with each other. Indeed, the study of that interaction forms the basis of the burgeoning young discipline of neuroendocrinology, one of the most exciting frontiers of modern biological science.

Elsewhere in this issue of the *Journal*, Dr. Ontjes brings us up to date regarding two of the latest discoveries in neuroendocrinology: the identification and synthesis of the releasing factors for ACTH (CRF) and for Growth Hormone (GRF). The magnitude of these undertakings is astounding — imagine dissecting and processing half a million sheep hypothalami to garner a few micrograms of purified peptide! But once a trace of the pure material is in hand, the mills of the protein chemists grind miraculously fast — the complete analysis of the GRF seemed to follow almost literally on the heels of the identification of a patient with GRF excess. Almost immediately after analysis came synthesis, so that now there are abundant supplies of syn-

thetic releasing factors ready to be pressed into experimental service as diagnostic reagents or to be used as probes to investigate basic endocrine physiology.

I would bet, however, that the most exciting clinical applications of these new compounds are yet to come. Look at the lessons we have learned from gonadotropin releasing factor (LHRH). It has been in experimental use for less than a decade and only this year achieved approval from the FDA for routine clinical use. In this brief span of time the pioneering studies of Knobil and his colleagues¹ have demonstrated that the beginnings of puberty are encoded in the cyclical secretion of LHRH by the hypothalamus. By mimicking those secretion cycles it is possible to initiate puberty in immature monkeys¹ or, as Crowley and his coworkers have shown, in human beings with hypogonadotropic hypogonadism.² On the other hand, sustained infusions of LHRH (or the use of long-lasting synthetic analogues) do not enhance gonadotropin secretion; in fact, they inhibit it. The observation that too much agonist actually impairs gonadotropin output led, in turn, to the use of a long-lived analogue of LHRH to stop the progress of idiopathic precocious puberty in humans.³ Thus, at least in the case of gonadotropin secretion, we now have the means to stimulate or suppress secretion. This blossoming ability to turn pituitary function on or off almost at will augurs a new era in the therapy of hormone disorders. We can hope that the future holds equally promising uses for CRF and GRF.

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From the Department of Medicine, Duke University Medical Center, Durham 27710.

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Corporate Restructuring: One Answer to TEFRA's Challenge

Paul M. Wiles

WHEN President Ronald Reagan signed TEFRA, the Tax Equity and Fiscal Responsibility Act, September 3, 1982 the Federal Government sent a clear signal to health care providers. The message: The Federal Government is no longer willing to pay costs of services that hospitals and other providers render to Medicare beneficiaries.

TEFRA, designed to save the government \$2.8 billion in 1983 and \$5.9 billion by 1985, culminates 17 years of tinkering with the Medicare payment system. By year's end, all Medicare-participating hospitals will have been subject to TEFRA constraints on operating costs per Medicare discharge. Further, nearly one-third of the hospitals will have entered the first year of the new Medicare prospective pricing program, with most of the others following as their new fiscal years begin in 1984.

From a political viewpoint, the Act satisfies taxpayers by reducing the Medicare cost liability without changing the benefit package offered to an increasingly vocal Medicare population. With passage of the Act, the government has told providers of health care to find their own solutions to the problem of inadequate funding. Solutions may include improved productivity and more efficient use of routine ancillary services in meeting patients' needs.

Recently, however, another solution has surfaced, corporate restructuring of nonprofit hospital groups. To understand why this option is being considered, it is important to understand the marketing dynamics facing hospitals today.

Medicare and the Graying of America

The root of the problem is the growing Medicare population, people over the age of 65. While the U.S. population will grow between 1980 and 1990 at an 8½% rate, the over 65 age category will increase at a rate of 21% in this decade, a rate two and a half times faster than the population as a whole. By 1990, the over 65 population will comprise 12.6% of the total U.S. population, up from 11.3% (table 1). This will mean that there will be 5,364,000 additional Medicare beneficiaries in the year 1990.

The significance of these numbers to both Social Security administrators and health providers is that the over 65 population uses hospital care three to eight times more than the under 65 population. In 1980 the under 65 population used 860 days of hospitalization per thousand population, the age category between 65 and 74 used 2,580 patient

TABLE 1
U.S. Population (000)

	Total	65 and Over	65 and Over, %
1970	205,052	20,107	9.8
1980	227,658	25,708	11.3
1990	247,000	31,072	12.6

Source: U.S. Bureau of the Census, Current Population Reports, Series P-25, No. 922, "Projections of the Population of the U.S.: 1982 to 2050," U.S. Government Printing Office, Washington, D.C., 1982.

days, and the 75 and over population used 6,880 patient days per thousand population. The over 65 population, with its growth rate of two and a half times faster than the population as a whole and its higher hospital utilization rates, will be consuming hospitalization resources at rates ten times greater than those persons under the age of 65. This utilization rate clearly presents a cost of care problem for both the Congress and the nation. In the past, Congress has dealt with these problems by adopting laws and regulations that reduce the outflow of dollars to hospitals and other providers. Congress has concentrated on payments to health care providers and has been careful to avoid reducing the scope of services to the beneficiaries of the Medicare program. This is obviously an astute political decision that bodes ill for the future financial viability of institutional health providers.

The Growth in Cost Shifting

Since its inception, Medicare has paid hospitals on a cost reimbursement basis. The cost to be reimbursed is derived using a Medicare cost allocation process. This process has consistently produced a growing gap between a hospital's full operating cost and the "allowable cost" paid by Medicare. With the called-for savings in TEFRA, this difference will become even greater. In order to cover these unreimbursed costs, hospitals have traditionally played the role of Robin Hood, that is, by cost shifting these nonpayments from the Medicare system to patients who were sponsored by commercial insurance or who pay their own hospital bills. Table 2 shows that the percent of hospital charges reimbursed to hospitals by the Medicare system has declined from 75.4% in 1974 to 68.7% by 1981. The savings called for by TEFRA are likely to reduce that difference between hospital charges and hospital payments to 60.8% by the year 1985.

The new prospective price system, which became effective October 1, 1983, was established by Public Law 98-

From the Forsyth County Hospital Authority, Inc., 3333 Silas Creek Parkway, Winston-Salem, NC 27103.

TABLE 2
Hospital Charges and Medicare Payments, 1974-1981

Year	Hospital Charges Per Day	Hospital Reimbursement By Medicare	Difference in Dollars	Percent Of Total
1974	\$120	\$ 90.48	\$ 29.52	75.4
1975	145	108.90	36.10	75.1
1976	171	127.40	43.60	74.5
1977	197	144.20	52.80	73.2
1978	225	162.23	62.77	72.1
1979	255	181.56	73.44	71.2
1980	294	204.62	89.38	69.6
1981	334	229.46	\$104.54	68.7

Source: Office of Statistics and Data Management, Bureau of Data Management and Strategy, Health Care Financing Administration

21, the Social Security Act Amendments of 1983. The Act requires payment to hospitals on a diagnostically related group basis. While this would seem to be a more equitable method of reimbursing hospitals, the Act calls for "budget neutrality," meaning that payment should be no greater than the payment would have been under the Tax Equity and Fiscal Responsibility Act of 1982. Thus, we can continue to project the Medicare reimbursement shortfall, even under this new revised payment system.

Competition for Other Patients

Other factors facing the hospital provider in the balance of this decade are competition, cost containment, need for alternative delivery systems, and the growth of multi-institutional arrangements. Most of these factors have, at least as a part of their genesis, the Medicare reimbursement problem. There will be growing competition between health providers for the patients who are privately sponsored by commercial health insurance or who are responsible because of the nature of the service for their own health care payments. Traditionally, these patients have borne the Medicare shortfall. If hospitals are not able to compete in a cost-effective way for these patients, little or no cost shifting possibilities will remain. Medicare shortfalls will cause hospitals to be even more seriously underfunded. This underfunding will create a two-tiered medical system in which the aged and poor will be treated in facilities able to produce only the level of care commensurate with the payments from federal or state sources. Privately sponsored patients will be treated in facilities that accept few, if any, Medicare patients, and thus, at a lower cost since there will be no cost shifting burden.

Cost escalation in the health care marketplace is an issue that has demanded great public attention. Industry and business leaders have only recently begun to address the cost of their health care benefit packages. In the coming years they will attempt to find alternative methods of providing high quality medical care to their employees without having to underwrite the ever increasing burden of cost shifting. This will lead industrial and business purchasers of health care services to new forms of delivery mechanisms. The recent rapid growth of ambulatory surgery centers and freestanding emergency or immediate care facilities are two examples where costs are lower than similar hospital services and thus economically more attractive, assuming the quality of care to be equal for the treatment required.

Alternative delivery systems, such as those mentioned above, will also compete to satisfy consumer demand.

The consuming public between the ages of 19 and 64 is already indicating its desire for geographically convenient, noninstitutional care. In addition to surgery and immediate care centers, freestanding birthing and wellness promotion centers will provide needed medical services in nontraditional ways.

And finally, hospitals, in an attempt to meet all of these issues, will find themselves more closely aligned through multi-institutional arrangements. From mergers of two or more health providers, to affiliations of multiple providers, hospitals will join to receive the benefits of economies of scale in purchasing, management specialization and other cost saving programs.

The Restructuring Option

One strategy to deal with these problems or opportunities is restructuring. To understand corporate restructuring one must know how hospitals have been organized and owned over the past 30 to 40 years. Generally, hospitals fall into one of four categories. The largest single group of hospitals is known as private nonprofit hospitals. These organizations are generally membership corporations where the members appoint a board of trustees or serve themselves as a board of trustees of a single hospital provider.

Since 1968 there has been a significant growth of the second group, for-profit hospital corporations. These corporations, many of which are listed on the New York Stock Exchange, own or manage for others up to several hundred hospitals. Each of the corporation hospitals is a profit center directed by an administrator working under centralized corporate controls.

The third type of hospital organization is municipal hospital ownership, found predominantly in the South and inner city sections of major metropolitan areas. These hospitals may be owned by a city or county government and operated either by that government or through legal arrangements such as a lease to a not-for-profit corporation.

And finally, state and federal governments operate various kinds of specialty hospitals; for instance, mental health facilities and public health hospitals.

The common factor among private nonprofit hospitals is that traditionally the board of trustees has had as its sole purpose and function the operation of a single hospital provider within the community. Many institutions recognize that this corporate structure can no longer maintain the hospital's market position within its community. This is why over the past five years a good deal of discussion and action has taken place about corporate restructuring, or as it is sometimes referred to, corporate reorganization.

Corporate restructuring of hospital providers attempts to satisfy all or some of the following objectives:

- 1) To maintain a single standard of quality medical care to all patients without regard to the patient's financial status or third party payer.
- 2) To develop multiple capital sources. Without capital funds, it will be impossible for hospitals to replace their facilities and equipment or to fund new technological enhancements or programs. Restructuring,

then, will address itself to all forms of capital generation, philanthropy, new revenue sources, improved debt capacity, and even joint ventures or equity funding.

- 3) To develop new or additional sources of revenue. With the Federal Government paying less for services rendered to their beneficiaries, and with patients requiring new delivery systems, hospitals are finding it necessary to compete in new markets to generate funds to cover federal nonpayments or to provide new services demanded by patients.
- 4) To avoid burdensome federal and state regulations. In the past, the Federal Government has used the regulatory process to reduce its payments to hospitals. A number of states have adopted rate setting to control health care costs. A proper restructuring plan will reduce the exposure of the constituent organizations to these regulations, as well as the current health planning regulations.
- 5) To maximize reimbursement. As regulatory processes become more rigid and reimbursements decline, the organizational structure should capture every lawful dollar of reimbursement for the hospital. Reorganized hospitals find that reimbursement is modestly affected. Any change, however, means that the community bears a smaller cost shifting burden.
- 6) To maintain a stable governance mechanism. Multi-corporate restructuring plans should serve to improve communication, planning, and control of all of the organizations. Generally, overall control is done by one board of trustees through the adoption of system-wide policies, while individual boards are responsible for specific functions, thus enhancing their knowledge base and shortening the lines of communication.

Corporate restructuring, or the legal rearranging of a hospital and its related components, generally takes the form of a foundation, a merger, or a parent holding company.

Hospitals of all sizes across the country have restructured by creating foundations, nonprofit corporations under the Internal Revenue Service Code. Foundations are relatively simple to establish and operate. They meet many of the above objectives of restructuring.

The Benefits of Foundations

Foundations have as their principal objective the creation of additional funds through philanthropy. By being separately incorporated they can shelter philanthropic funds from offsets in reimbursement or from rate setters. Through their own forces or subsidiaries they may also operate activities which under reasonable circumstances would be considered normal hospital businesses. These services may include collection of delinquent hospital accounts, physician billing services, the operation of the hospital's snack shop, and other services. Funds raised by the foundation, either through philanthropy or services, can then be contributed to the hospital so they will have minimum adverse impact on reimbursement.

Hospitals use two types of foundations when restructuring. The first is a related foundation (figure 1), where the



Figure 1. Related foundation.

board of trustees of the foundation is controlled, generally through appointment power, by the hospital's board of trustees. A related foundation must contribute funds exclusively to the hospital.

The second type of foundation, which is not used as often in restructuring, is an unrelated foundation (figure 2). This kind of foundation remains independent of the hospital and can use its funds for any charitable endeavor. In order to maintain its nonprofit status with the IRS, it is held to a much higher standard of charitable giving.

Foundations pose some challenges for hospital administrators. Related foundations may be vulnerable when assets are consolidated. Regulators or rate setters could consider the foundation's assets the same as the assets of the hospital and thus offset or reduce hospital reimbursements.

A hospital organization with an unrelated foundation has its own problem — two independent boards of trustees. Coordinated governance becomes difficult.

The Parent Holding Company

The ultimate form of corporate reorganization is known as the parent holding company (figure 3), an entity resembling a financial or bank holding company.

The parent holding company most nearly meets all of the six objectives of corporate restructuring. Most important, it allows for flexible responses to the changing health care environment while sheltering non-hospital or non-provider activities from regulators and rate setters. Of course, it still provides coordinated governance and management.

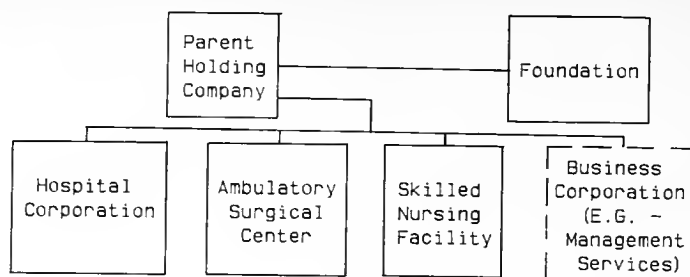
Under a parent holding company, the hospital becomes a subsidiary to the parent corporation. In most cases, both the parent company and the hospital subsidiary are nonprofit organizations. The parent company is responsible for setting corporate-wide policy. It may have other subsidiary organizations both within the health care area and outside, such as proprietary businesses.

The parent company governs through the appointment of boards of trustees or boards of directors at each of the subsidiaries. The board sets financial goals for each subsidiary and is the only body that can amend the articles of incorporation or bylaws of subsidiary corporations. Too, trustees are responsible for long range planning and development of lines of business within the entire corporate structure.

Reorganization experts generally consider the parent holding company the superior form of corporate reorganization because it offers the benefits of control of the



Figure 2. Unrelated foundation.



— Tax Exempt Corporation

-- Taxable Corporation

Figure 3. Parent holding company.

organization without the liability of consolidation of financial resources in a health care provider. When the balance sheet is consolidated at the parent holding company, the asset and revenue resources are unavailable for offsets by third party payors — the parent holding company is not a direct health care provider itself. Revenues generated in subsidiaries are also sheltered from offsets by federal regulators. In order for the regulators to change this situation, they will have to attack an entire body of corporate law, affecting not only health care holding companies, but also many proprietary corporations that have wholly owned corporate subsidiaries.

After subsidiaries pay their appropriate taxes they can dividend their profits to the nonprofit parent company which in turn can use those profits for the shortfall in Medicare reimbursement to its hospital subsidiaries. The result is a reduction in the cost shifting burden to the community, and consequently, lower charges. The hospital becomes more competitive with providers who are not required to provide care through the Medicare Program.

Involving the Medical Staff

Medical staffs of hospitals should be involved in the restructuring process with the administration of the hospital

and its trustees. Generally, the staff should support a restructuring program because, if successful, the hospital will be better able to provide a single level of high quality medical care regardless of the patient's financial sponsor. This, of course, is the objective of physicians in delivering their own health care.

One danger of corporate restructuring, however, is that the hospital and its medical staff may find themselves in direct competition. This situation can usually be avoided through open and frank discussions about the needs of the hospital and the physicians. Enlightened hospital management will recognize the futility of direct head-to-head competition with its medical staff and will attempt to build mutually satisfactory arrangements to provide needed health care services in the community without confrontations with the medical staff.

A Complex Solution for Complex Problems

The need for corporate restructuring arises from complex marketing, regulatory and financial needs. The process of restructuring is also complex in its legal and accounting design as well as in its operation. For certain hospital systems, however, restructuring deserves careful consideration of the issues and the potential solutions it offers.

Medicaid Payments for Nursing Home Services in North Carolina

C. Wayne Stallings

THE decade of the 1970s witnessed an explosion in the number of persons receiving long term nursing care in North Carolina. In 1970 there were only 8,265 nursing home beds in our state. By 1982 the number of beds had increased to 21,034 divided into two distinct levels of care: Skilled Nursing Facilities (SNF), which provide intensive convalescent services, and Intermediate Care Facilities (ICF), which provide less intense service to patients whose physical condition, though reasonably good, requires them to receive continual monitoring and physical support that cannot be provided at home. Fifty-seven percent of the nursing home beds are licensed to provide intermediate care.

There are several reasons for the large growth in nursing services. First, because modern medicine has made it possible for us to live longer, an ever growing proportion of our population is reaching the age where nursing care is likely to be needed. The vast majority (87%) of those who receive institutional nursing care are elderly persons, suffering the effects of serious age-related debilitating illnesses such as strokes, broken bones, diabetes, Alzheimer's disease and the like. The typical nursing home patient is 75 years of age. In 1970 North Carolina had 412,038 citizens over 65 (8.1% of the population). By 1980 this number had swelled to 601,831 (10.2% of our population of 5,881,766). As the number of elderly candidates for nursing care grew, the demand for institutional nursing care also grew. Demographic projections tell us that this growth will continue well into the next century.

Second, changes in family structure and size have made it more difficult for the elderly to convalesce at home. Many nursing home residents have no close relatives. Some have children who are themselves elderly, or nearly so. An 85-year-old woman's children are likely to be in their 60s. Family members may live very far away from their elderly relative, having moved from their hometown or county to get good jobs. Extended families are smaller because of the trend toward fewer children, so the number of persons available to share the financial and physical burden of caring for an elderly relative needing convalescent care is smaller than in the past. In most younger households all the adult members are employed outside the home, leaving no one to care for an elderly relative should it become necessary. Finally, many nursing home patients

have very complex medical problems that untrained family members are unable to treat adequately in the home and home health services in the community may not be readily available or affordable.

Despite the limitations on family and home care, however, a very small percentage of the elderly actually require institutional nursing services. Only about 5% of the elderly received care in a nursing home in 1980 although 39% were ill enough to require hospitalization. Clearly, family and friends still play a large role in helping the elderly recover from serious illness.

Third, in our view the most important cause for the expansion of institutional nursing care has been the emergence and growth of public financing through the Medicaid and, to a lesser extent, the Medicare programs. Close to 90% of all nursing care is paid for by these two programs, with the great majority being financed by Medicaid.

Medicare is the publically supported health care insurance program for the elderly and disabled that began in 1965. The goal of Medicare is to relieve the elderly and disabled of the excessive financial burdens of serious illness. Following traditional health insurance patterns, Medicare focuses its attention on the costs of acute care received in hospitals. Eligible persons may also pay an additional premium to receive Medicare coverage for physician care and similar outpatient services. However, Medicare will support only a limited amount of nursing care in a Skilled Nursing Facility. After 100 days in a nursing home the patient must pay the bill from his own resources if he needs further care. If the patient needs intermediate care rather than skilled care Medicare pays nothing.

This limited coverage of nursing home care by Medicare has forced the Medicaid program to shoulder the lions' share of the cost. The Medicaid program was instituted by the Congress in 1965 to provide the poor with access to medical and health care services. Unlike Medicare, which is available to Social Security recipients regardless of their income, Medicaid recipients must be virtually destitute to qualify. Persons receiving cash assistance from programs such as Aid for Dependent Children or Supplemental Security Income are usually automatically eligible for Medicaid benefits. In addition, in North Carolina we permit persons who are not receiving cash assistance to become eligible for Medicaid benefits when their outlays for medical and health care services reduce their financial resources below the poverty level. These persons are called the "medically needy."

From the North Carolina Division of Medical Assistance, Department of Human Resources, 410 N. Boylan Avenue, Raleigh 27603.

Institutional nursing care services have been supported by the Medicaid program since its inception; however, the Program has never imposed the strict limits on coverage of these services that Medicare does. Rather, Medicaid has always paid for an unlimited number of days of care if they were medically justified. Medicaid thereby has become the financial "safety net" for those elderly and disabled persons who need nursing care but haven't the financial resources to pay for it. The financial burden of nursing care that Medicare avoids very often falls upon Medicaid, because relatively few of the elderly and disabled pensioners in our state have the money to pay for the expensive medical and nursing care they need for the full duration of a spell of severe illness and subsequent convalescence.

The North Carolina Medicaid program began paying for skilled nursing care in 1970. Intermediate care was added in 1974 in an effort to reduce the cost per day of care for those persons who still needed nursing service, but at a less intense level than that provided in a skilled facility. Figures 1 and 2 depict the very substantial growth in both the number and cost of nursing care days of service paid for by Medicaid since its inception. From a modest beginning of \$16.5 million in 1971, the first full year in which Medicaid services were offered in North Carolina, the program grew elevenfold to 1983's expenditures of \$181.2 million. In the coming year we expect to exceed \$200 million in outlays for nursing home services.

The ICF program that was introduced in 1974 to contain cost had, by 1976, grown to be larger than the SNF program and has remained so until the current year. Figure 1 shows how the introduction of ICF care did slow, and for two years actually reverse, the growth in the number of SNF days of care purchased by the Medicaid program. This gain was quickly offset by the extremely rapid growth in the number of ICF days of care and the steep inflation in the daily cost of care that struck in the late 1970s (see figure 3).

These growth trends indicate the massive investment in nursing homes that was occurring in the middle and late

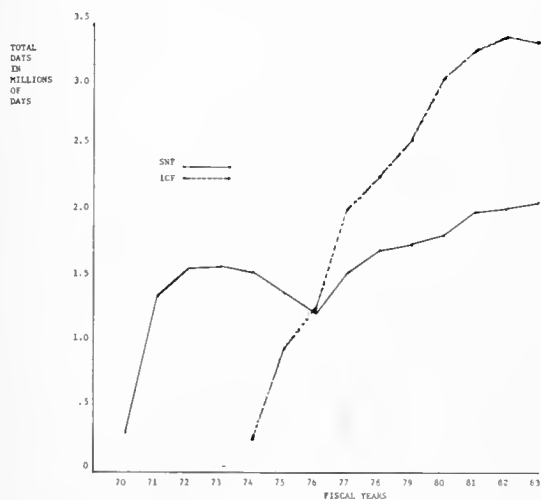


Figure 1. Growth in the number of nursing care days paid for by Medicaid — 1970-1983.

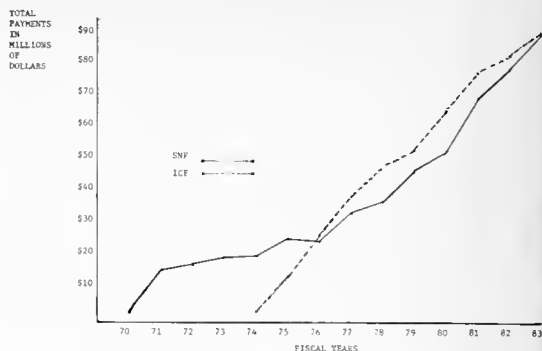
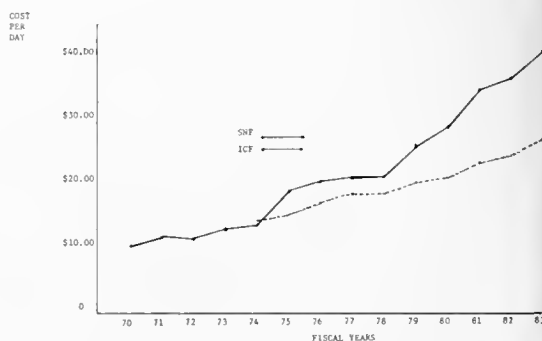


Figure 2. Growth in Medicaid payments for nursing care — 1970-1983.

1970s. The large, but formerly latent, demand for nursing services combined with the steady funding source in the Medicaid program to create very attractive investment opportunities that rapidly drew capital into the industry. Nursing home chains, both large and small, sprang into existence. Competition for labor and materials among health care institutions (including both nursing homes and hospitals) intensified, driving up per diem costs at the same time that the number of beds was increasing.

The methods for determining how much Medicare and Medicaid would pay nursing homes for their services exacerbated these inflationary pressures. In its early years Medicare adopted the philosophy that it would pay hospitals and nursing homes only their actual costs incurred in providing care to Medicare patients. Medicaid programs generally followed this lead. At the time this approach seemed conservative. The charges of nursing homes and hospitals were generally set above the cost of care to return a profit or surplus. Paying only cost was cheaper. For a time, when the Medicare proportion of the total days of care provided in hospitals and nursing homes was relatively small, this approach made sense. Market forces, i.e., the unwillingness of private patients to pay excessive charges from these institutions, could be relied upon to keep costs reasonable.

Health care market conditions shifted rapidly in the early



1/ Daily costs do not include amounts that must be paid from the patient's own resources.

Figure 3. Growth in daily cost of nursing home services — 1970-1983.¹

1970s, however, as a growing proportion of patients turned to Medicare, Medicaid and other health insurance programs to pay for their care. In North Carolina today, Medicare and Medicaid pay for about half of the days of care in hospitals and nearly 90% of the care in nursing homes. With this shift in payment responsibilities from the individual patient to public programs, market pressure to contain costs evaporated. The availability of Medicare and Medicaid funds to finance care enabled many more patients to avail themselves of scarce health care resources, and consequently the prices of these resources increased rapidly. Cost-based reimbursement allowed these large increases in the cost of care to be passed through directly to the taxpayers.

The entrepreneurial environment produced in the nursing home industry by the rapid growth in facilities combined with cost-based reimbursement to foster a variety of financial abuses aimed at maximizing short term profits. Facilities were sold and resold among related parties to pyramid capital costs that could be passed on to Medicare and Medicaid. Inflated lease back arrangements for buildings and equipment were created with similar intent. Mortgages were refinanced frequently increasing interest costs to the public while providing cash windfalls to the mortgagee. Lucrative contracts were signed among related persons to acquire management service of dubious value but at great price. All these abuses contributed to the inflationary spiral in nursing home costs. And, while they did not characterize the industry as a whole, they nevertheless were sufficiently prominent to attract the attention of public officials in our state.

The response of North Carolina policy makers to the rapid increases in the cost of nursing care began to take shape in 1976. At that time the General Assembly declared a freeze on nursing home rates that was to remain in effect until a new method for determining those rates could be implemented. This new method of payment was to cast aside the reasonable cost "pass-through" form of reimbursement inherited from Medicare in order to contain costs.

Pursuant to the 1976 legislation, the Department of Human Resources enacted a prospective reimbursement plan in 1977. The plan was called "prospective" because it set payment levels in advance of services being provided. Under reasonable cost reimbursement final payment levels could not be determined until after services had been provided and actual costs were ascertained. This was called "retrospective" reimbursement. The initial prospective reimbursement plan remained in effect with some modification until January 1980 when the current plan became effective.

The current reimbursement plan for nursing services attempts to achieve three goals:

- (1) To support good patient care.
- (2) To contain all costs, but particularly administrative and property costs, within reasonable bounds.
- (3) To permit a reasonable profit to investors but eliminate financial manipulations that produce excessive profits.

To achieve these goals, the plan contains several unique features that will be described in the following paragraphs.

The current plan sets a reimbursement rate for each nursing home for each level of care. We currently enroll 39 facilities that provide only skilled nursing care and 65 that provide only intermediate care. Each of these facilities has one rate. We also enroll 123 facilities that provide both skilled and intermediate care. These facilities have two rates, one for each level of care.

The rates are based upon the actual reasonable costs incurred by the nursing homes in the year 1978. Homes that have begun operations since 1978 have rates based on their costs in the year they became active. We have been using the cost data from 1978 as the basis for the rates since the inception of the current plan in 1980. The purpose in using the same base for so many years is to establish consistent expectations among nursing home operators about their financial future. This stability enables them to make the long term investments in plant and services needed to improve patient care. It also builds the confidence investors need to overcome the excessive concentration on short term profits that brought on the abuses of the middle 1970s. As we enter our fifth year under the current plan we have seen a growing stability in the nursing home industry in North Carolina that is proving beneficial to patient care.

Each nursing home's rate is divided into two parts, one part to pay for direct patient care services such as nursing care, food service, laundry and linens and various therapies (called the "direct" cost rate), and a second rate to cover property related costs (depreciation, interest, leases, maintenance) and administrative overhead (called the "indirect" cost rate). Although these two components of the total rate are based on 1978 cost data, they are computed separately and affect reimbursement in quite different ways.

To compute these rates 1978 costs for SNF services and ICF services were separated. Next the per diem direct and indirect costs for each nursing home were computed. These per diem costs were then ranked separately from the lowest to the highest. (See table 1 for an example.)

After ranking the direct costs, the 75th percentile of cost was identified. We established this amount as the maximum cost we would allow as a basis for future rates. Each nursing home was given a direct patient care rate based on its actual direct cost in 1978 or the maximum allowable cost (75th percentile of cost), whichever was lower. The per diem direct cost for each home was then adjusted upward by 10% to encourage spending on direct patient care services. This adjustment provided each nursing home with additional funds that could be used to enrich nursing services, patient diets, patient activities, social services and therapy. We believe these additional funds have gone a long way toward fostering the favorable quality of nursing care that patients in this state receive. We know, for example, that most nursing homes now employ far more nurses and nursing aides than the minimum state licensing standards require.

In the indirect per diem cost ranking we identified the 60th percentile of cost (see table 1). This amount became the basis for the indirect rate for all nursing homes regardless of their actual cost. Thus, whereas each nursing home was assigned its own unique direct rate based on its 1978 direct costs, all homes supplying a particular level of care

TABLE 1
Sample Arrays of 1978 Per Diem Cost

Provider	1978 Per Diem Direct Cost	Provider	1978 Per Diem Indirect Cost
<i>Skilled Nursing Facilities</i>			
Home A	\$21.10	Home B	\$10.90
Home B	20.89 75th Percentile	Home C	10.80
Home C	20.18	Home E	10.45 60th Percentile
Home D	20.04	Home A	9.50
Home E	19.50	Home D	8.90
<i>Intermediate Care Facilities</i>			
Home J	\$15.06	Home L	\$9.10
Home K	14.41 75th Percentile	Home M	9.02
Home L	13.80	Home K	8.94 60th Percentile
Home M	13.20	Home N	8.50
Home N	12.90	Home j	8.26

(SNF or ICF) were given the same indirect rate.

Both the adjusted direct costs and the indirect costs from 1978 are adjusted for inflation that has occurred since 1978 to establish the rate that will apply in a given year. To make this adjustment we use inflation factors that reflect the change in prices actually being experienced in the nursing home industry rather than some broad and imprecise measure such as the Consumer Price Index. In fact we even develop separate inflation adjustment factors for the direct and indirect rates because a large portion of indirect costs are fixed, such as building depreciation and mortgage interest, and therefore deserve no inflation adjustment. Table 2 lists the inflation factors that have been used to adjust the 1978 costs to 1982-83 fiscal year levels. Table 3 shows how a nursing home rate is computed using these factors.

We pay the computed rates to each nursing home for an entire year. At the end of that year each home must file an extensive report detailing its actual costs incurred during the year by the type of cost (e.g., salaries, materials) and service area (e.g., nursing, food service, administration). Using these reports we compare the actual costs expended on direct patient care services by each home with its direct rate. If a home's direct expenditures fall below the direct rate, the unexpended funds must be paid back to the Medicaid program. This feature of our reimbursement plan helps ensure that the funds provided by the program for vital patient care services are not directed to other purposes. The patients get the benefit.

We also compare actual indirect costs with the indirect rate. This comparison is made for information purposes

only, however, because we permit each provider to retain all the indirect rate regardless of its actual costs. Thus, a home whose indirect costs exceed the indirect rate loses money. A home whose costs fall below the rate makes a profit. Each provider must earn its profit by keeping its property and administrative costs within reasonable bounds. It cannot profit by reducing vital patient care services.

We believe that our current reimbursement system for institutional nursing care has produced the favorable results it intended. First, in a period of high inflation, the increase in nursing home rates in North Carolina has been held below national inflation (see table 2). Second, we have given needed financial stability to an industry that had been buffeted by frequent shifts in reimbursement policy. Consequently, we have seen many of the abusive practices used in the past to maximize short term profits dwindle away. Instead, we have established a funding base that permits reasonable long term profits. In FY 1982 the average nursing home profit margin was a modest 6%. Third, and most important, vital patient care services have been maintained and enhanced.

As we look to the future of nursing care reimbursement we face many challenges. The need for care seems to be expanding at a faster rate than we can afford. We must find less expensive ways to get the job done.

For the near future, institutional care in nursing homes will remain the principal means for delivering nursing care. But, an increasing emphasis will be placed on home and community-based alternatives that enable patients to con-

Table 2
Long Term Care Inflation Allowances Compared to Broad Measures of Inflation

	Nursing Home Inflation Rates			CPI %	CPI Medical Care Component
	Direct %	Indirect %	Weighted Average		
1978 Base					
1979	9.1	9.1	9.1	11.8	9.2
1980	8.0	8.0	8.0	12.7	11.0
1981	9.9	7.0	8.9	11.0	11.5
1982	8.2	5.8	7.3	5.0	11.4
1983	6.7	5.0	6.1	2.4	8.4
Cumulative % Increase	49.0	40.0	46.0	50.0	63.0

Table 3
Examples of Nursing Home Rate Calculations

	Direct	Indirect	Total
Nursing Home C. (SNF)			
1978 Base	\$20.18	\$10.45	
Patient Care Incentive	<u>× 1.10</u>	<u>× 1.19</u>	
Adjusted Base	\$22.20	\$10.45	\$32.65
Inflation Adjustments			
1978 to 1979	× 1.091	× 1.091	
1979 to 1980	× 1.080	× 1.080	
1980 to 1981	× 1.099	× 1.070	
1981 to 1982	× 1.082	× 1.058	
1982 to 1983	<u>× 1.067</u>	<u>× 1.050</u>	
1982-1983 Rate	\$33.19	\$14.63	\$47.82
Nursing Home J. (ICF)			
1978 Base	\$14.41	\$ 8.94	
Patient Care Incentive	<u>× 1.10</u>	<u>× 1.00</u>	
Adjusted Base	\$15.85	\$8.94	
Inflation Adjustments			
1978 to 1979	× 1.091	× 1.091	
1979 to 1980	× 1.080	× 1.080	
1980 to 1981	× 1.099	× 1.070	
1981 to 1982	× 1.082	× 1.058	
1982 to 1983	<u>× 1.067</u>	<u>× 1.050</u>	
1982-1983 Rate	\$23.70	\$12.51	\$36.21

valesce at home. New organizational forms and service delivery methods will have to be developed, perhaps combining professional services with the assistance of family, friends and volunteers. With these new forms new reimbursement techniques will have to be evolved to finance adequate services while discouraging waste.

In nursing home reimbursement itself, we can also expect changes. In the near term we will probably have to update our rate base from 1978 costs to costs in a more recent year because, as time passes, changes in nursing home service delivery are pushing the 1978 cost structure toward obsolescence. When we make the change, adjustments in the direct/indirect rate composition and computation methods will probably be necessary to protect the

achievements of the current plan.

Over the longer term we will have to consider some difficult issues such as more direct links between individual patient conditions and reimbursement rates, the extended family's financial responsibility for the care of elderly relatives, and the possibility of encouraging a measure of price competition among similar nursing homes.

Whatever the result of these challenges we have learned that a well conceived reimbursement policy is a powerful tool not only to limit expenses, but also to encourage the rational use of financial resources and high quality patient care. We hope to build upon this knowledge in meeting these future challenges.



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Babies Hospital, 1920-1978

Lockert B. Mason, M.D.

BABIES Hospital in New Hanover County opened its doors in 1920 to serve sick infants and children without regard to ability to pay or county of residence. It began with twenty-two beds and enlarged over the years to sixty beds. It ceased operation in 1978.

The hospital was not the earliest concern for the needs of sick children in southeastern North Carolina. In the late 19th and early 20th centuries the salubrious effect of sea-breezes was widely acclaimed. In 1896, James Sprunt, author and philanthropist, stated, "It is a matter of fact that salt sea air will often do more good to a sick, puny child than any of the medical remedies in the pharmacopoeia. Many anxious, worn out mothers have had reason to bless Captain Harper as the means under providence of restoring to health their sick or feeble little ones. A beloved physician has often said that daily trips from Wilmington to Southport are even more beneficial to sick children than a residence on the seashore. The gliding motion of the boat soothes them, the clear fresh air of the river invigorates and strengthens them, and the entire freedom from dust and grime which is so disagreeable and hurtful on railroad journeys brings grateful sensations of cleanliness and comfort to young and old alike."¹

The reference is to the steamer *Wilmington* which made daily trips from Wilmington down the Cape Fear River to Southport, a distance of about 20 miles, leaving at 10 A.M. and returning at 5 P.M. At that time Captain John Harper had completed more than 13,000 trips between Wilmington and Southport and was considered the most popular man in Wilmington (figure 1).² The *Wilmington* was built in 1882, and was 139 feet long, could carry 650 passengers, and had a top speed of 17 miles per hour. Sick babies from the up country and the city were taken on the trip to benefit from the sea breezes. About 1910 the trips were continued on the Steamer *Southport*. Shortly thereafter, the custom was discontinued as "all too often these little sufferers became an unwelcome nuisance."³ Evidently some of the children died on the trip and this was the nature of the nuisance.

The need for special care for infants was greatest during the summer months because of the prevalence of diarrhea and dehydration caused by lack of screens, abundance of flies, and inadequate refrigeration of milk which was fed after the infant was weaned.

In 1915, Dr. J. Buren Sidbury established practice in Wilmington after postgraduate training in pediatrics in New York City. Within a year his practice had grown to the



Figure 1. The steamer *Wilmington*; Captain Harper, insert.

extent that he limited it entirely to pediatrics, thus becoming the second pediatrician in North Carolina following Dr. Albert S. Root of Raleigh. In the spring of 1920, Dr. Sidbury purchased a large wooden cottage and surrounding land overlooking Wrightsville Sound and Wrightsville Beach (figure 2). He appealed to the citizens of the area to assist in furnishing the hospital to provide care for sick infants and children regardless of county of residence and ability to pay. In his appeal he cited the success of seaside resort hospitals for the treatment of sick babies and children in Atlantic City, Hugenot, New York, Cape May and Virginia Beach. Individual contributions from one dollar to one thousand dollars totaled \$3,773.39 in the first year. In addition, there were gifts of furniture for a nurses' office, five cots, half bushel of potatoes, two cans of disinfectant and fly killer, two weeks supply of milk, linen, flat silver and dishes, baby carriages and go-cart, chiffonier and cribs. (The cost of endowing a charity bed for the summer was \$200.)

The Babies Hospital opened on June 6, 1920. It contained twenty-two beds, seven of which were designated for charity patients. During the first season there were 83 patients, 14 of whom were charity and the per diem cost was \$3.42. Within the hospital was a milk station capable of preparing any prescribed scientific feeding. In addition to serving the patients in the hospital this milk service was made available for babies in the surrounding area, a great convenience to families visiting Wrightsville Beach and Wrightsville Sound. During the first summer 1,200 feedings were prepared for babies outside the hospital. The hospital closed at the end of the season and continued to operate only in the summer months until 1939.

In 1921, an annex to include eight additional beds was

From the Department of Surgery, New Hanover Memorial Hospital and the Department of Surgery, University of North Carolina School of Medicine.



Figure 2. *Original Babies Hospital.*

added. In 1924, a second annex was added to include a dining room. Dr. Sidbury recognized the importance of the psychological support of having the mother stay with the baby and accommodations for mothers in the rooms with their children was arranged in 1922 and continued throughout the existence of the hospital.

On Sunday, May 29, 1927 the hospital was demolished by fire and the nine patients were transferred to the James Walker Memorial Hospital in Wilmington. At that time the counties adjacent to New Hanover made no provision for hospital care of indigent children and the James Walker Memorial Hospital was not supposed to accept charity cases from outside New Hanover County. For this reason it was urgent that an alternative arrangement be made. A few hours after the fire the Board of Directors of the Babies Hospital met and decided to resume operations in another cottage on Wrightsville Sound which had been made available for a dollar for the remainder of the season through the

generosity of the Murchison Bank and its president, Mr. J. V. Grainger. On September 23, 1927, a certificate of incorporation was amended to meet the needs of a new hospital as a nonprofit stock corporation. In December 1927, a contract was let for a two story fireproof hospital which opened on June 15, 1928, having been constructed with funds from insurance on the old building and from donations by public subscriptions (figure 3).

Beginning in 1939, the hospital remained open year round. Hurricane Hazel struck October 15, 1954 at high tide. Buses at the back door were prepared to remove the patients when necessary. Dr. Sidbury delayed the decision because he believed the building to be one of the safest in New Hanover County. The Atlantic Ocean completely covered Wrightsville Beach and reached the first step of the front porch of the hospital. The waters then receded and evacuation was not necessary. The hospital served temporarily as a headquarters for the Red Cross, Salvation Army,



Figure 3. *Babies Hospital 1928.*

and other rescue workers.

In 1954, there were 1969 admissions and an appeal was made for contributions to enlarge the hospital adding more beds and two new operating rooms. The addition of a third floor, which was made possible by a large contribution from Mrs. Jessie Kenan Wise and donations by other friends, was dedicated on July 8, 1956.

The Willie Daniel Sidbury Nurses Home was constructed behind the main building in 1955, a gift of Dr. Sidbury as a memorial to his wife.

Again through the generosity of Mrs. Jessie Kenan Wise another building was constructed on the property to house a pediatric research center and was dedicated in December 1962. Dr. Daniel C. Darrow was the first director of the research center and continued his life-long study of fluid and electrolyte balance. Following his death in 1965 it became advisable to change direction of the research and it became a marine biomedical research laboratory under the direction of Dr. Ralph Brauer with the cooperation of the Deans of Duke University Medical School, Bowman Gray School of Medicine, and the University of North Carolina School of Medicine. In 1971 the facility was donated to the University of North Carolina at Wilmington and continues as the Institute for Marine Biomedical Research.

Realizing the need for nurses with special training in the problems of sick children Dr. Sidbury (figure 4) began to offer training to outstanding graduates of the James Walker Nursing School in 1928. Many of these nurses became pediatric supervisors in hospitals of North and South Carolina. From 1942 until 1967 the hospital conducted a nurses training program to which senior student nurses from hos-

pitals throughout the state were sent for three months of pediatric training.

An approved pediatric residency was conducted until about 1965. A number of pediatricians now practicing in North Carolina and elsewhere trained at Babies Hospital. After the residency was discontinued an elective rotation was offered to interns from James Walker Memorial Hospital in Wilmington.

The year 1967 was of greatest usage with average daily census of 42 patients of which 2.8% were free days according to the Duke Endowment definition. In the previous and following years free days were 7.7% and 7.8%. The aberration in 1967 is not explained. Progress in prevention and treatment of children's diseases replaced the efficacious sea breezes and diminished the necessity for hospitalization of infants and children. Average daily census declined to 17 in 1977, the last full year of operation. It became evident that the need for a pediatric hospital was diminished and the Board of Directors elected to close the hospital in mid 1978. In its fifty-eight years of existence no tax monies were used in the construction or operation of Babies Hospital. Thus ended an era in which a nonprofit hospital for treatment of private and indigent patients could be built and operated without assistance of tax funds. For the first fifty years there was no Medicaid to help pay for the charity patient. The Duke Endowment gave \$1 a day for each day of indigent care for many years. In the depression of the 1930s this was approximately twenty-five per cent of the per diem cost. In 1955 the Ford Foundation gave an unsolicited \$40,000 as part of its program of assistance to hospitals without tax support. The building was sold after 1978 and now is used for offices (figure 5). Assets of Babies Hospital, Inc. are managed as a charitable foundation supporting health care for children.

Dr. Sidbury was Medical Director of the hospital from its beginning until his death in January 1967. Early in his practice he had established milk stations in Wilmington to prevent summer diarrhea. He recommended early operation for congenital hypertrophic pyloric stenosis.³ With the participation of surgeons Thomas Green, James Robertson, and Joseph Hooper, Donald Koonce, and others more than 100 patients were operated upon. He made the diagnosis, corrected dehydration, and often administered anesthesia. In 1923 he reported using the umbilical vein for transfusion of the newborn⁵ and later used this route for exchange transfusion in neonatal jaundice. Dr. Sidbury's reputation resulted in an inordinately large referral area. Although Babies Hospital served eastern North and South Carolina primarily it was not unusual for patients to come from other east coast states.

The first president of Babies Hospital, Inc. was Mr. Thomas H. Wright. He was followed by Mr. Thomas H. Wright, Jr., Mr. Walker Taylor, III, and Lt. Gen. (ret) George S. Boylan.

An account of Babies Hospital would be incomplete without mentioning Miss Alice K. Schulken who was the Superintendent of the Hospital and of Nurses for 27 years. The title does not include that she also planned the meals, did the purchasing, supervised housekeeping and grounds including an outstanding rose garden, often working 18 hour days 7 days a week.



Figure 4. Dr. Sidbury 1928.



Figure 5. Babies Hospital Building, 1983.

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3. Unpublished Manuscript, "History of Babies Hospital," author unknown, in possession of Miss Willa Dickey.
- 4 Green TM, Sidbury JB. Hypertrophic stenosis of the pylorus in infants. *Surg Gynec & Obst* 159-164, Feb. 1919.
5. Sidbury JB: Transfusion through the umbilical vein in hemorrhage of the new born. *Am J Dis Child* 25:290-296, 1923.

Acknowledgment

The author expresses thanks to Miss Willa Dickey for providing much of the material on which this account is based, to Mr. Ashley Gale, Jr., of the Duke Endowment for statistical information, to Lt. Gen. George Boylan for additional information, and to Mr. Geoffrey Honaker for photography.

ADDENDUM

Life with Father

James B. Sidbury, M.D.

IT was a rather serious business. He was dedicated totally to pediatrics but it was quite clear to his children that he took his responsibilities as a father quite seriously. He was remarkably flexible in his approach to rearing but was inflexible in his belief in the importance of education.

His one avocation was quail hunting. He was good at it. Even when he hunted a full day it didn't seem to tire him. I was often invited along. I did tire and I was a wretched shot. I suspect the only quail I ever "shot" were those he shot and gave me credit. The salutary aspect of the hunting trips insofar as I was concerned was the traveling to and from the hunt. These were some of the rare occasions we would have together. The conversation usually drifted to medicine or teachers he had known and how they had influenced his life.

As an adult I learned he was really quite a different person from the stoic and spartan individual I had known as a child.

He really had quite a good sense of humor; dry, a bit droll, but a good sense of humor. My favorite story is one told to me in part by Mr. Steve Harwood in the comptroller's office at Duke University.

My father had been a virtual walking medical text book the last two years of his life; having one condition after

another. Enough to destroy the sense of humor of most men. He had a number of stays at the Duke Medical Center.

On the occasion of one of his admissions I contacted Dr. Barnes Woodhall, who was then Dean or Provost, and told him he should approach my father about giving money to establish a chair in Pediatrics. I told him that my father would not take it seriously if it came from me. Dr. Woodhall was successful. A day was decided when the transaction was to take place. My father with a paper bag, Dr. Woodhall and Dr. Anlyan met and went to Mr. Harwood's office to deliver the securities which would establish the Pediatric Professorship. They arrived at Mr. Harwood's office; the paper bag was proffered. Mr. Harwood, replete with green shade, counted the securities. He looked up and said, "Dr. Sidbury, that's not enough." Whereupon my father reached into his right inside pocket and introduced additional securities. Dr. Woodhall and Dr. Anlyan were terribly embarrassed. Mr. Harwood counted the additional securities and said, "Dr. Sidbury, that's still not enough." My father calmly pulled additional securities from his left inside pocket. Conversation at this point was indeed a bit awkward. Mr. Harwood counted and noted the total was sufficient. Few would ever have suspected my father was capable of such a practical joke, especially not Dr. Woodhall or Dr. Anlyan. It also illustrates what the poor Deans and Provosts have to handle in the pursuit of money!

Forty-five Years with Dr. Sidbury

Villa M. Dickey

ON June 6, 1933 I arrived by train in Wilmington to spend three months working with Dr. Sidbury at his offices in town and at the Babies Hospital. I rode the street car to the front yard of the hospital on Wrightsville Sound just across the Inland Waterway from the beach. For a number of years that was the main transportation for the hospital staff. My three months extended until the hospital closed 45 years later. To me, Babies Hospital and Dr. Sidbury were synonymous.

Each fall he spent several weeks at one of the leading pediatric institutions keeping up with advancing technology. One of the first oxygen tents in North Carolina was made locally following instructions brought back from his "vacation." There were no oxygen gauges at that time.

Most of the pediatric problems requiring unusually intensive study were referred to Boston, New York, Philadelphia, Baltimore, St. Louis, or Richmond. When Duke Hospital began operations Babies Hospital was still the state's pediatric center. Partly to remedy this, Dr. Sidbury was appointed to the Board of Directors of Duke and served in that capacity for many years. He referred more and more patients there each year.

He gave the first doses of tetanus toxoid in North Carolina. Soon after receiving his booster dose, a doctor's child suffered a depressed compound skull fracture. The drug was so new that neither the surgeon nor Dr. Sidbury was willing to trust the toxoid and antitoxin was given.

The first dose of streptomycin given in North Carolina was to a little patient from the Lake Waccamaw area.

At one of the meetings of the North Carolina Pediatric Society held at Babies Hospital, Dr. W. C. Davison and Dr. Sidbury presented the question of mandatory administration of DPT. Dr. Davison was unanimously asked to follow up on this and a state law was soon enacted.

Resident physicians from Yale, New York, St. Louis Children's Hospital, Philadelphia and Johns Hopkins were sent on a rotating basis so that they might become more

accustomed to dealing with private practice and with mothers staying with their sick children. This assured Babies Hospital of an excellent resident at all times.

For many years, Dr. Sidbury was the only member of the American Pediatric Society not associated with a large hospital or teaching institution.

Many poliomyelitis and diphtheria patients owe their lives to treatment received at Babies Hospital, and I owe much of the satisfaction of my life to the same institution, its staff members, its patients, but particularly to its founder and director, Dr. J. Buren Sidbury (Figure 6).



Figure 6. Photograph of a portrait of Dr. Sidbury.

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biopsy or cytologic confirmation of the diagnosis. Patients who have metastases outside the mediastinum or who have had previous treatment are not eligible.

To refer a patient or to obtain further information, call or write David N. Danforth, Jr., M.D., Admitting Officer, Surgery Branch, National Cancer Institute, Building 10, Room 10N119, Bethesda, MD 20205. 301/496-1533.

North Carolina Names in the News

The North Carolina Division of the American Cancer Society held its annual meeting on October 29-30 and elected new officers. New President is Walter B. Love, Jr. of Monroe; Chairman of the Board is Avery McMurry, M.D., of Shelby. Other officers elected were Charles L. Spurr, M.D., of Winston-Salem, President-Elect; Ruth Dublin of Smithfield, First Vice President; Lawrence K. Boggs, M.D., of Charlotte, Second Vice President; Johnnie Setzer of Claremont, Secretary; Wesley Allen, M.D., of Fayetteville, Assistant Secretary; J. T. Lindley of Raleigh, Treasurer; H. John Hatcher of Raleigh, Assistant Treasurer; and Roger O'Quinn of Raleigh, Executive Vice President.

The Eye-Bank Association of America, Inc. awarded **Lawrence B. Holt, M.D.**, of Winston-Salem the R. Townly Paton Award for distinguished service rendered the world in the development of the eye-bank movement. Dr. Holt founded the North Carolina Eye and Human Tissue Bank and helped found the Eye-Bank Association of America, of which he was the first ophthalmologist-president.

The North Carolina Surgical Association held its fall meeting at The Greenbrier in White Sulphur Springs, West Virginia, September 29-October 2. Their officers for this year are **Dr. Fred Taylor**, President; **Dr. James Davis**, Vice-President; **Dr. Henry Wilson**, Secretary-Treasurer.

Continuing Medical Education

Please note: 1. The Continuing Medical Education Programs at Bowman Gray, Duke, East Carolina and UNC Schools of Medicine, Dorothea Dix, and Burroughs Wellcome Company are accredited by the American Medical Association. Therefore CME programs sponsored or cosponsored by these schools automatically qualify for AMA Category 1 credit toward the AMA's Physician Recognition Award, and for North Carolina Medical Society Category A credit. Where AAFP credit has been obtained, this also is indicated.

IN STATE

January 1984

"Advanced Seminar for Certification in Administrative Psychiatry"

Place: Chapel Hill

Credit: 32 hours

Info: Malinda Marsh, Department of Community Psychiatry, UNC School of Medicine, Wing D, 208H, Chapel Hill 27514. 919/966-5277

February 3-4

"Live from Duke — Pediatrics 1984"

Place: Durham

Credit: 11.5 hours, Category 1 AMA; PREP

Info: Cindi Easterling, Box 3306, Duke University Medical Center, Durham 27710. 919/684-6485

February 6

"Records and Other Necessities"

Place: New Bern

Info: Wayne Parker, Medical Mutual Insurance Company, Box 27444, Raleigh 27611. 919/828-9334

February 17-18

"Clinical Teaching"

Place: Chapel Hill

Fee: \$275.00

Credit: 12

Info: Ms. Ruth De Bliek, ORDEHP, UNC School of Medicine, 322 MacNider Bldg. 202H, Chapel Hill 27514. 919/966-3641

February 19-22

"Beyond Advanced Clinical Teaching Skills"

Place: Rougemont

Credit: 20 hours Category 1 AMA

Info: Dr. Katharine Munning, 407 Crutchfield Street, Durham 27705. 919/471-2571

February 20-22

"Selected Topics for the Practicing Clinician"

Place: Durham

Credit: 24 hours Category 1 AMA

Info: Cindi Easterling, Box 3306, Duke University Medical Center, Durham 27710. 919/684-6485

February 24-26

"NCSIM/NC-ACP Joint Meeting"

Place: Greenville

Info: Kathy Adams, North Carolina Medical Society, Box 27167, Raleigh 27611. 919/833-3836

March 1-3

"2nd Annual Diving Accident Symposium"

Place: Durham

Credit: AMA, AAFP, ACEP

Info: Cindi Easterling, Box 3306, Duke University Medical Center, Durham 27710. 919 684-6485

March 6

"Duke Tuesday"

Place: Durham

Credit: 5 hours Category I AMA

Info: Linda Mace, Box 3707, Duke University Medical Center, Durham 27710. 919 684-2033

March 7-10

"Internal Medicine: 1984"

Place: Chapel Hill

Credit: 25 hours AMA Category I

Fee: \$250.00

Info: William B. Wood, M.D., 231 MacNider Bldg 202H, UNC School of Medicine, Chapel Hill 27514. 919 962-2118

March 15-16

"Eighth Annual Cancer Research Symposium"

Place: Chapel Hill

Credit: 11 hours AMA Category I

Info: Mrs. Mimi Minkoff, Cancer Research Center, UNC School of Medicine, Chapel Hill 27514. 919 966-3036

March 18-21

"Improving Residency Rotations: Curriculum Planning and Negotiation"

Place: Rougemont

Credit: 20 hours Category I AMA

Info: Dr. Katharine Munning, 407 Crutchfield Street, Durham 27705. 919 471-2571

March 28-31

"Clinical Epidemiology"

Place: Chapel Hill

Credit: 24 hours

Info: Ruth De Blik, 322 MacNider Bldg. 202H, UNC School of Medicine, Chapel Hill 27514. 919 966-3641

April 7

"13th Annual New Bern Symposium: Infectious Disease"

Place: New Bern

Info: William B. Hunt, Jr., M.D., Box 2157, New Bern. 919 633-8607

April 8-11

"Administrative Skills: Faculty as Managers"

Place: Rougemont

Credit: 20 Hours Category I AMA

Info: Dr. Katharine Munning, 407 Crutchfield Street, Durham 27705. 919 471-2571

April 10

"37th Annual Medical Symposium: Pulmonary Medicine"

Place: Greensboro

Info: L. S. Slotnick, M.D., 1018 North Elm Street, Greensboro 27401. 919 275-7238

April 11-14

"3rd Annual Spring OB-GYN Symposium"

Place: Durham

Credit: AMA, ACOG

Info: Cindi Easterling, Box 3306, Duke University Medical Center, Durham 27710. 919 684-6485

April 12

"North Carolina Neuro-ophthalmology Review"

Place: Chapel Hill

Credit: 2.5 hours Category I AMA

Info: Baird S. Grimson, M.D., UNC School of Medicine, Chapel Hill 27514

April 20-21

"Carolina Outcome Workshop"

Place: Chapel Hill

Credit: 13 hours Category I AMA

Info: David E. Eifrig, M.D., UNC School of Medicine, Chapel Hill 27514.

OUT OF STATE**February 5-11**

"Winter Conference in Internal Medicine"

Place: Snowshoe, VA

Credit: 20 hours Category I AMA

Info: Cindi Easterling, Box 3306, Duke University Medical Center, Durham 27710. 919 684-6485

February 12-17

"Postgraduate Course in Diagnostic Imaging"

Place: Cancun, Mexico

Fee: \$475

Credit: 25 hours Category I AMA

Info: Donald R. Kirks, M.D., Box 3834, Duke University Medical Center, Durham 27710. 919 681-2711, ext. 286 or 287

February 20-22

"Gold Coast Seminar: Surgery"

Place: West Palm Beach, FL

Credit: AMA, AAFP

Info: Continuing Medical Education, Box 3306, Duke University Medical Center, Durham 27710. 919 684-6485

February 22-25

"Medical Computing"

Place: Key Biscayne, FL

Credit: AMA, AAFP

Info: Cindi Easterling, Box 3306, Duke University Medical Center, Durham 27710. 919 684-6485

March 4-10

"Sports Medicine"

Place: Snowshoe, WVA

Credit: 20 hours AMA Category I

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March 5-7

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Place: West Palm Beach, FL

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Place: Hilton Head, SC

Credit: 20 hours Category I AMA

Info: Joan K. Erpf. 316/379-0191

April 9-11

"Gold Coast Seminar: OB-GYN"

Place: West Palm Beach, FL

Credit: AMA, AAFP

Info: Continuing Medical Education, Box 3306, Duke University Medical Center, Durham 27710. 919 684-6485

In Memoriam

Edgar Vernon Benbow

Edgar Vernon Benbow, M.D., died at his home in Winston-Salem July 18, 1983 at the age of 84. He was a graduate of East Bend High School, the University of North Carolina, its two year Medical School and Jefferson Medical College. He interned and had residency training in Brooklyn Hospital and did post graduate work at the University of Pennsylvania and the University of Vienna. He served as Private in World War I and Major in World War II.

He was a diplomate of the American Board of Surgery and a qualified fellow of the International College of Surgeons. He did distinguished general surgical practice in Winston-Salem for thirty-one years and retired in 1958. He was twice President of the Staff at Baptist Hospital and twice Chief of Staff at City Memorial Hospital.

He was a member of the Oasis Temple of the Mystic Shrine and a member of Centenary Methodist Church. He was successful in business and gave generously to the Yadkin County Public Library, Guilford College, and the University of North Carolina.

He is survived by his wife Sue Satterwhite Benbow, children Carolyn, Vernon, and William and five grandchildren.

John H. Rosser, M.D.

John H. Rosser, M.D. died on June 23, 1983. Dr. Rosser attended Wheaton College in Wheaton, Illinois, received his medical degree from the University of Maryland in 1947, and then served a surgical residency at Emergency Hospital, Washington, D.C., Women's Hospital in Baltimore, Maryland, and the University Hospital at the University of Maryland. He served in the United States Air Force from 1950 to 1953.

He established his practice in Statesville in 1955, where he practiced until his death.

He served the medical community as a member of the American Medical Association, the North Carolina Medi-

cal Society, and the Iredell County Medical Society, and was a Fellow of American College of Surgeons. He served his community in various capacities, including being a Deacon of the First Baptist Church and chairman of that body for many years. He is survived by his widow, Pearl; his daughters, Deborah Kesler and Susan Wittig; and his sons, David and Dr. Stephen.

Charles Baynes Wilkerson, Jr., M.D.

Dr. Charles Wilkerson, beloved Raleigh internist, died on April 29, 1983, at the age of 64.

He was a graduate of the University of North Carolina and the Medical College of Virginia. He served an internship and residency at Rex Hospital before entering the U.S. Army immediately after World War II. On his return, he completed his training in Internal Medicine in the V.A. Hospital system, and then came back to Raleigh to join his sister, Annie Louise, in practice.

As evidence of his interest in high standards of education and practice, he served for six years as a member of the North Carolina Board of Medical Examiners, including one year as Chairman. He was also a past president of the Rex Hospital Staff and of the Raleigh Academy of Medicine.

Dr. Wilkerson was also interested in driver safety. He was the original and only Chairman of the State's Driver Medical Review Board set up in 1967 legislation to evaluate the competence of drivers with health problems. His colleagues in practice, in the Division of Health Services, in the Department of Motor Vehicles, and in the Attorney General's Office were quick to praise his objectivity, thoroughness and fairness.

He was a life-long member of the Edenton Street United Methodist Church. He had served as President of its governing body and was the current President of its Endowment Fund.

Dr. Wilkerson is survived by his wife Lib, his daughter Beth, sisters Annie Louise and Margaret Flint, and brother Louis.

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proof that it's people who give people the will to live. The work in the lab must continue. And so must the work outside. We need your help.

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Letters to the Editor

An Appliance for the Blind

To the Editor:

I was pleased to see the October issue of the *North Carolina Medical Journal* with its patient section devoted to information to help patients with visual problems that cannot be corrected. My sister has recently become blind. She had no way of determining the time of day; on awakening from sleep she didn't know whether it was morning or night. We bought an alarm clock from Radio Shack that tells the time audibly every hour on the hour or whenever the button on its top is depressed. It is available from most Radio Shack stores or through their catalog for \$39.95. A suction cup attached to the bottom of the clock so that it won't be knocked off the table by a sleepy hand would be helpful.

Alice Cleland
Methodist Retirement Home
Durham 27705

The Ophthalmology Issue

Dear Doctor Hughes: (one of the Editor's bosses)

How kind of you to seek me out at the Homestead and comment so kindly on the *Virginia Medical Journal*. It was ever so generous of you.

On my return I made my way to your October issue with the ophthalmologic theme — an excellent issue, beautifully put together and presented. And what a good idea, to publish not only for your doctors but for their patients! Toward which worthy goal your "Features for Patients," pages 645-656, is simply splendid, with its lively drawings and helpful information. My compliments!

Ann Gray, Executive Editor
Virginia Medical Journal
4205 Dover Road
Richmond, VA

Oozing and Bruising

To the Editor:

I wish to compliment Dr. John Stuart and Virginia Burnette on their November scientific article. This discussion of von Willebrand disease and qualitative platelet defect was concise, clear and pertinent — just the ticket for practicing surgeons. Keep up the good work!

Randall D. Johnson, M.D.
16 McDowell Street
Asheville 28801

Long-term Results in Spastic Dysphonia

To the Editor:

In the June 1983 issue, an article entitled "Spastic Dysphonia Helped By Clipping Recurrent Laryngeal Nerve" by Drs. Patrick D. Kenan and John E. Riski was of considerable interest but I felt did not quite go far enough. Certainly the recurrent laryngeal nerve section for spastic dysphonia has gotten considerable publicity in the head and neck literature but may not have been well publicized in

other fields. However at this time, there are reports now being published raising question as to the long-term results. Drs. Dedo and Izdebski reported that a majority of patients reported subjective improvement in their voices immediately, and four years postoperatively, 80% gave unqualified recommendation for the operation while 20% expressed some reservation about the surgical treatment of spastic dysphonia (*Laryngoscope* 93:9-16, 1983).

Drs. Aronson and DeSanto found that after three years only 36% of the patients had any improvement in voice as compared with preoperatively and a significant percentage of patients had a voice that was classified as worse than before surgery. They concluded that recurrent laryngeal nerve surgery for adductor spastic dysphonia has long-term limitations (*Laryngoscope* 93:1-8, 1983).

I have found it important in my practice to inform patients of these long-term consequences and results. I likewise feel it is important when we report to our colleagues that these results be given as well so as not to perhaps falsely raise the patient's hopes and expectations.

William B. Costenbader, M.D.
131 McDowell Street
Asheville 28801

Dr. Kenan replies:

Thank you for allowing me the opportunity to review the material sent you by my friend, Dr. William Costenbader. With his characteristic thoroughness, he has nicely crystallized some of the important long-term issues associated with the management of spastic dysphonia.

I am familiar with the papers he mentioned in his letter. Of the two, the paper by Dedo has, I believe, greater merit for several reasons. First, Dedo is the originator of the technique of the recurrent laryngeal nerve section for the treatment of carefully selected patients with spastic dysphonia. Second, he probably has the largest series of patients so treated of anyone in the world. And third, recognizing that this technique is not a cure-all for all such cases, he is very careful in his selection of patients for operative treatment. This paper does indeed mention alternate forms of treatment including removing the edge of the vocal folds by CO₂ laser or the use of teflon injection of the folds. His results of 80% improvement four years or more following nerve section represent to me a very positive endorsement of this technique. In comparison, the smaller series by Aronson and DeSanto registers a success rate of only 36%. Even this rate of success has a certain merit because it translates into one out of three successes in comparison with almost a 0% success rate for speech therapy or psychotherapy as the only treatment modality.

Dr. Costenbader is quite right in emphasizing the need to inform patients of long-term results. I would emphasize again the standard diagnostic test is a Xylocaine injection of the left recurrent laryngeal nerve with noting of the immediate effects thereof. Others have emphasized that even a good result using an anesthetic agent might well justify a repeat effort with a placebo injection of sterile saline in

order to separate the purely psychogenic problems from the truly neurogenic.

In summary, very careful patient selection remains the most important criterion in choosing patients for the recurrent laryngeal nerve section and each patient so selected must be informed that at best there are four out of five chances for long-term benefit.

Patrick D. Kenan, M.D.
Duke Hospital
Durham 27710

An Anlyan Story

To the Editor:

I attended the Duke University Medical School Alumni Reunion (Class of '48) recently and would like to congratulate Dr. William Anlyan on the honors he received during the Reunion. The Central Tower of the new hospital was named in his honor.

This recognition was just reward for the many things that Bill has accomplished for Duke University since he came to Duke after graduating from the Yale Medical School 33 years ago.

I would like to relate to you a story known only to a few surgeons which involved the destiny of Dr. Anlyan and to honor and enhance the integrity of another of Duke's famous and beloved surgical teachers, Dr. Deryl Hart, who was chairman of the Department of Surgery at that time.

In 1951 the Korean War erupted and five of the surgical house staff residents (Drs. Gordon Carver, Marcus Dillon, Robert Gowdy, Eugene Lindberg, and Glenn Young), who were two years ahead of Dr. Anlyan in the surgical training rotation, volunteered and went to the Armed Forces. Dr. Anlyan was rejected by the armed services because of his ankylosing spondylitis. Two years later those five who had been in service returned to complete their surgical residency at Duke, and Dr. Hart found himself with six men at the same level of training. A decision had to be made as to who was to be the first to go through the surgical residency and who would be last.

At that time Duke was graduating a surgical resident qualified in general, thoracic, and cardiovascular surgery every six months. Dr. Hart's dilemma was that if Dr. Anlyan followed the five men who were two years his senior in experience and training it meant two and a half years in the laboratory waiting to get back into the surgical service rotation. If Anlyan went first, each of the other five would be set back only six months.

Dr. Hart solved the problem by calling these five young surgeons into his office, explaining the situation to them, and left them to decide Anlyan's fate. His parting remark was, "You men volunteered for and put your lives on the line for your country. I appreciate this very much, and you must decide whether Anlyan goes through the program first or last."

It meant only a six-month delay for each of us or a two and a half year delay for Bill. We decided to let Dr. Anlyan go first through the residency ahead of us. I think we had a premonition that he might go back to Yale if he had to wait, and we didn't want to lose him. His contributions to Surgery and to Duke proved this to have been a good decision.

I don't know whether Dr. Hart revealed the intricacies of this decision to Dr. Anlyan. Perhaps Dr. Anlyan will respond to this letter.

Gordon M. Carver, M.D.
1202 Broad Street
Durham 27705

A Davison Story

To the Editor:

I think that the *Journal* can stand one more Davison letter.

In 1936 I had been dating a Miss Mary Carter who was an assistant head nurse on one of the Duke wards. She had recently been hired by Dr. Max Oates, surgeon, who had finished his residency in 1936 and was going back to his home town of Martinsburg, West Virginia where his father owned the hospital. They were planning to add pediatric beds and a nursery to the hospital. I was asked to come to Martinsburg and help with some of the details. I decided to go up to see Miss Carter and look over the hospital before deciding about working in Martinsburg. The problem was that I had no means for traveling to West Virginia.

Carl Rogers saw that I was really concerned about something and asked what was bothering me. (Carl Rogers was a black man called, by Dave, the assistant dean.) I told him that I wanted to make a trip to Martinsburg to see my girlfriend and look over the hospital there. He asked what I was worried about; I said that I didn't have any money to go up there but guessed I could borrow it from someone. Carl said, "Wait a few minutes, Dr. Gay," and returned in 10-15 minutes saying that Dr. Davison had agreed to let me borrow his car to go to West Virginia. Then Carl asked me if I had money to buy gas and I told him no, but I guessed I could borrow that from some of my friends. Carl said, "Wait a few minutes," and he came back in about 15 minutes and said that Dr. Davison was going to let him fill up the car with gas and lend me \$10 to help me with the gas up and with other expenses. Gas was less expensive in 1936.

On the way up the radiator began leaking. I had not thought to check the radiator for water. It was therefore necessary for me to stop at different houses along the route and get water and my getting to Martinsburg was delayed. When I arrived I took the car to an automobile mechanic who said he could fix it for \$10. Of course there was nothing else I could do but let him go ahead and fix it. In the meantime, Dr. Oates had been nice enough to say I could stay in one of the hospital rooms, therefore I did not need a hotel room.

Miss Carter and I, of course, had lots of fun looking over the hospital and city together although we did not have any money to spend. I returned safely back to Duke University Hospital having decided that I would accept Dr. Oates' invitation and go up for one to two years while they were finishing the wards.

A followup on this story has to do with 1948 when the Pediatric Society was having its annual meeting at Roaring Gap and Dr. Davison was the speaker. As secretary to the Society I was sitting next to Dave at Dinner. In the course of conversation, he asked me how I was getting along in Charlotte, and I said, "Pretty well. I am actually making a

little money." Dr. Davison took out a little black book which he kept notes in and turned to a certain page and looked at me and said, "Well, maybe you are doing well enough that you can pay back the \$10 you borrowed from me back in 1936." Of course, I was a little embarrassed although I hadn't actually forgotten; I just didn't feel I was getting along that well. Anyway, when I got home I sent Dr. Davison a check for the \$10 plus 6% interest for the years in between. Dr. Davison wrote me a note saying he

appreciated the \$10 but he had not intended to charge interest; however, since I had sent it he would give it to his favorite charity.

As a further followup, Miss Carter became Mrs. Gay June 29, 1937. We've been married 47 years.

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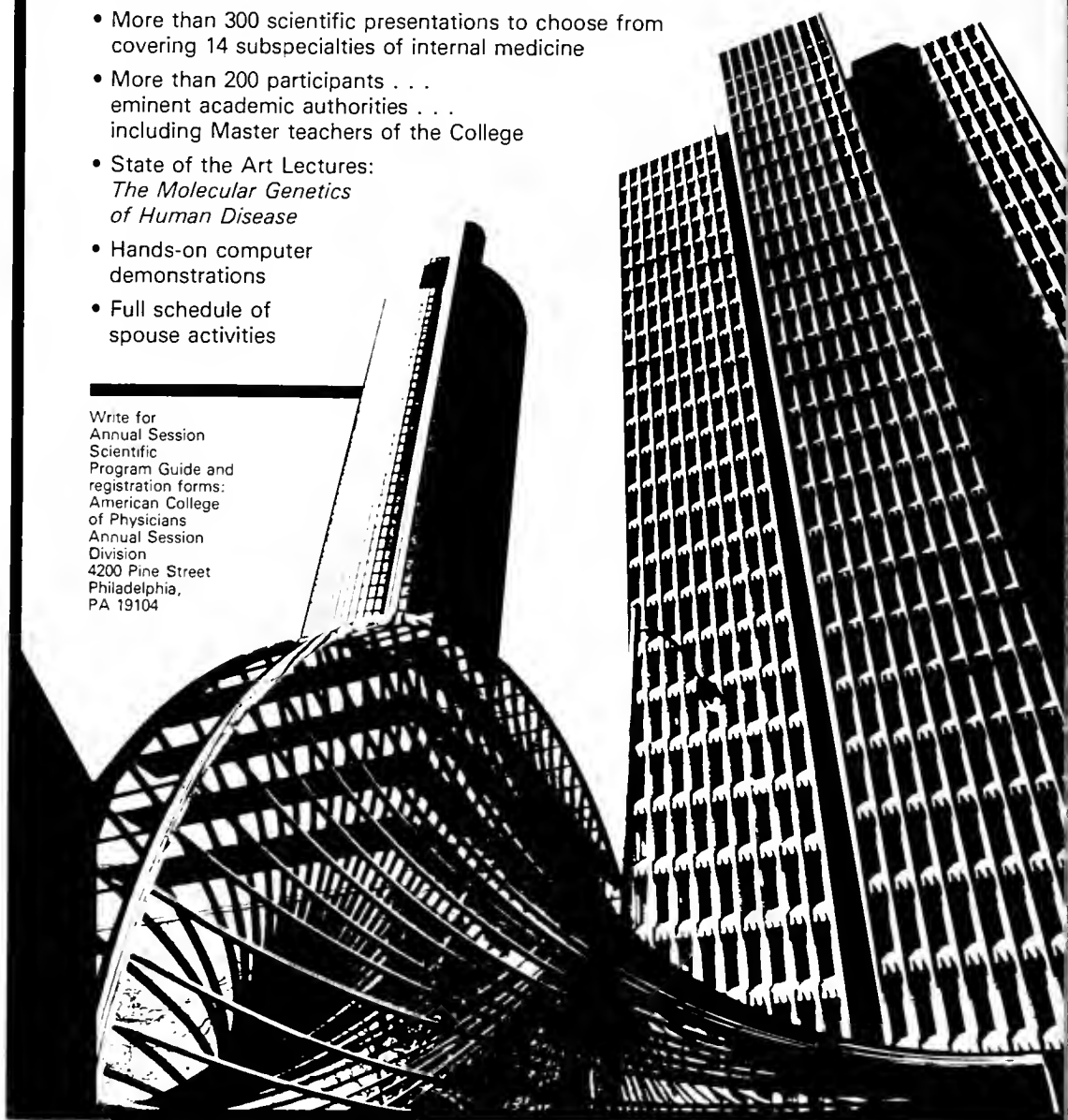
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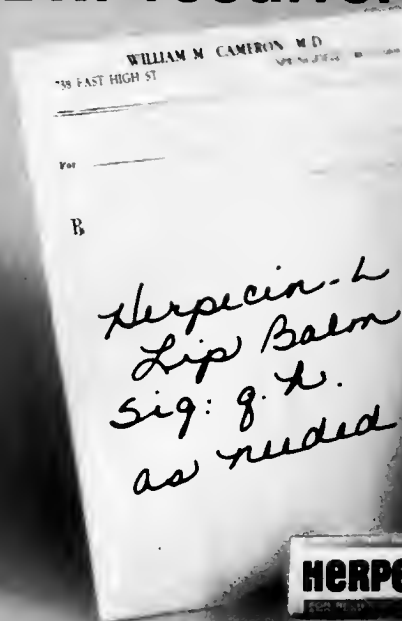
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sleep laboratory in the investigation of sleep and sleep disturbances. Scientific exhibit at the 124th annual meeting of the American Psychiatric Association, Washington, DC, May 3-7, 1971. 12. Pollak CP, McGregor PA, Weitzman ED: The effects of flurazepam on daytime sleep after acute sleep-wake cycle reversal. Presented at the 15th annual meeting of the Association for Psychophysiological Study of Sleep, Edinburgh, Scotland, June 30-July 4, 1975. 13. Data on file, Hoffmann-La Roche Inc., Nutley, NJ.

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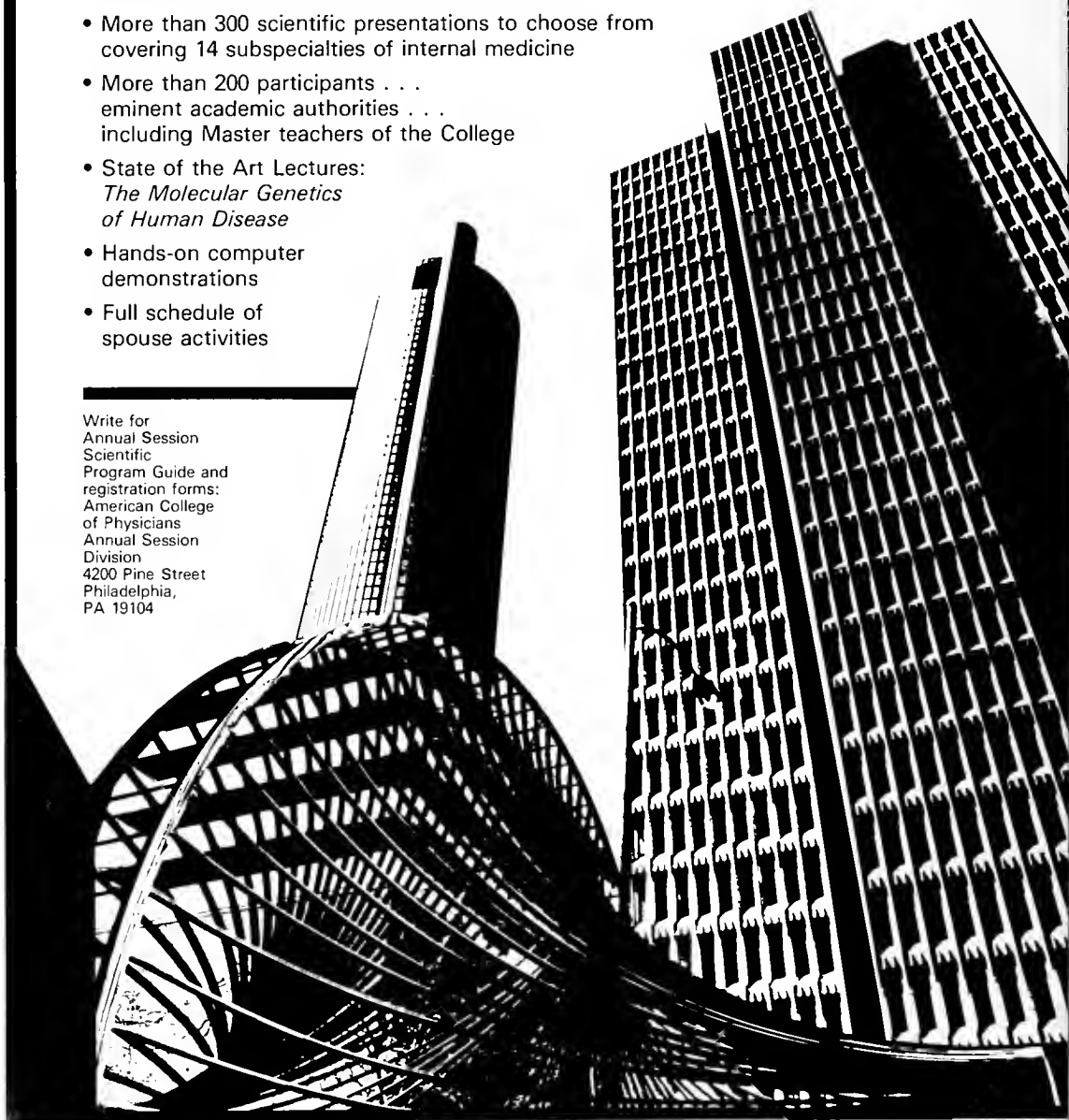
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An added complication... in the treatment of bacterial bronchitis



Brief Summary Consult the package literature for prescribing information

Indications and Usage Cefaclor* (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Lower respiratory infections including pneumonia caused by *Streptococcus pneumoniae* (*Diplococcus pneumoniae*), *Haemophilus influenzae*, and *S. pyogenes* (group A beta-hemolytic streptococcus). Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Cefaclor.

Contraindication Cefaclor is contraindicated in patients with an anaphylactic reaction to the cephalosporin group of antibiotics.

Warnings IN PENICILLIN SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS INCLUDING ANAPHYLAXIS TO BOTH DRUG CLASSES.

Antibiotics including Cefaclor should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics including macrolides, semisynthetic penicillins, and cephalosporins; therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life-threatening.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be ruled out.

Precautions **General Precautions**—If an allergic reaction to Cefaclor occurs, the drug should be discontinued and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

Prolonged use of Cefaclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Passive direct Coombs tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antioglobulin tests are performed on the minor, side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

Cefaclor should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

As a result of administration of Cefaclor, a false positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinette* tablets but not with Tes-Tape* Glucose Enzymatic Test Strip, USP, Lilly.

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Usage in Pregnancy—Pregnancy Category B—Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Cefaclor. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers—Small amounts of Cefaclor have been detected in mother's milk following administration of single 500-mg doses. Average levels were 0.18, 0.20, 0.21, and 0.16 mcg/ml at two, three, four, and five hours, respectively. Trace amounts were detected at one

Some ampicillin-resistant strains of *Haemophilus influenzae*—a recognized complication of bacterial bronchitis*—are sensitive to treatment with Cefaclor.¹⁻⁵

In clinical trials, patients with bacterial bronchitis due to susceptible strains of *Streptococcus pneumoniae*, *H. influenzae*, *S. pyogenes* (group A beta-hemolytic streptococci), or multiple organisms achieved a satisfactory clinical response with Cefaclor.⁷

Cefaclor
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hour. The effect on nursing infants is not known. Caution should be exercised when Cefaclor* (cefaclor, Lilly) is administered to a nursing woman.

Usage in Children—Safety and effectiveness of this product in infants less than one month of age have not been established.

Adverse Reactions Adverse effects considered related to therapy with Cefaclor are uncommon and are listed below.

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70).

Symptoms of pseudomembranous colitis may appear either before or after antibiotic treatment. Nausea and vomiting have been reported rarely.

Hypercutaneous reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100), pruritus, urticaria, and positive Coombs' tests each occurring in less than 1 in 100 patients. Cases of serum sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthralgia, myalgia, and frequently fever) have been reported. These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Cefaclor. Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain—Transient abnormalities in laboratory test results have been reported. Although they were uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic—Slight elevations of SGOT, SGPT, or alkaline phosphatase (1 in 40).

Hematologic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal—Slight elevations in BUN or serum creatinine (less than 500) or abnormal urinalysis (less than 1 in 200).

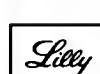
*Many authorities attribute acute infectious exacerbation of chronic bronchitis to either *S. pneumoniae* or *H. influenzae*.
Note: Cefaclor is contraindicated in patients with known allergy to cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

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Alcoholism Treatment Today

Jack Donovan, William J. Reid, M.D., Sherwood W. Barefoot, M.D.

ALCOHOLISM is society's most urgent yet neglected problem. We know progressive drinking means death for the alcoholic, but few appreciate that uncontrolled alcoholism can also mean death for society as we know it.

Thirty years ago the American Medical Association recognized alcoholism as a disease and not a moral insufficiency. Despite that observation, alcoholism still ravages the world, constrained only by the limited, yet effective, treatment available today.

Alcoholism destroys not only its victim but many persons surrounding the victim. The physical, emotional, and spiritual essence of a person dissipates even as an aggressive denial blocks sociomedical assistance. Painful stress begets a dependency on sedative relief; the entire cellular system known as a person becomes disoriented, irresponsible, and corrupt. A delusional state results, often presenting as psychoneurotic, confounding and disrupting relationships, careers, lives, society in general — denying, defying diagnosis — much less treatment.

Is it any wonder that society saw fit for centuries to ignore these "immoral deviants" and did little to prevent their spiritual disintegration?

Today, as many as 15% of us suffer this dynamic biochemical corruption called alcoholism — adversely affecting, directly or indirectly, nearly half of the earth's population and productivity.

Historically, society has found itself in a double-bind that has effectively blunted attempts to stem the destruction of alcoholism. Sales of alcohol account for an influential share of the gross national product. Despite society's habitual tendency to avoid self-imposed penalty at the expense of the few "deviants," new and specific legislation has been inspired by the painful experience of alcoholism's untold victims. Especially in the area of drunk driving, focus is concentrating on those whose behavior is dysfunctional, destructive, and unacceptable. Literally millions of offenders will be seeking treatment to resolve or at least ameliorate their "court-defined" drinking problem. By virtue of their advisory capacity, physicians will be involved because a disease is on trial. Physicians must be prepared to know the disease and methods of treatment.

An industrial reality now, alcoholism treatment came into being only recently in the long history of alcoholic dysfunction. If enthusiasm in the field can be equated with treatment effectiveness, success has been outstanding.

Treatment facilities vary in the specifics of their physical plants and programs but they generally subscribe to the *disease concept* providing abstinence as prerequisite of a rigorous program for physical health, self-evaluation/

reconciliation, and permanent remission through a reordering of spiritual values.

Briefly reviewed, treatment facilities (centers) share several basic characteristics.

General Setting. Whether skyscraper suite or rural cottage, facilities offer a certain bed capacity (30-60 average) usually portioned or segregated by sex, and sometimes as well for adolescent and geriatric, with 2 to 4 beds maintained for the acute care phase of early recovery. Some are physical extensions of medical or psychiatric hospitals, others free-standing; but in any case they are normally a medical setting adhering to requirements of the Joint Commission on Accreditation of Hospitals. Most often patients are monitored by nurses operating within the controlled environment. Primary effort is aimed at providing an unrestricted "community comfort" that enhances personal respect and self-discipline as a vital part of recovery. At least minimal housekeeping service is available at most facilities (more at some); however, many apply "participation" therapy involving the patient in service activity: cleaning, cooking, and such.

Recreation in posh treatment centers may include formal exercise, golf, swimming, and horseback riding. Equally successful facilities may provide only pool and/or cards. Patients seem to welcome the opportunity for visitation and meditation on the extensive grounds of suburban centers while others find enjoyment in occupational (arts/crafts) therapy. Appropriate audiovisuals are made available to the serious intellects. At the same time, special programs are provided for the exceptional patients.

Admission. Cooperation between the facility and the admitting physician is preferred, and imperative if treatment is to be effective. Patients treated for alcoholism in an Employee Assistance Program or by practicing physicians interested in alcoholism profit from the contact with doctors alert to the natural history of this disease and to family dynamics that may perpetuate the problem. Though some physicians need more experience in diagnosing, recognizing symptoms, and routinely requesting a drinking history, increasing numbers of doctors are accepting the reality of formal alcoholism treatment. Success rates of 75% plus which have been reported for persons treated in an Employee Assistant Program are creating more interest among the profession.

The goal of admission screening is to determine the patient's appropriateness for the available treatment regimen. Though most programs stipulate a minimum 3 to 4 weeks, all treatment is individualized and flexible to allow for extension or special attention as required in acute care patients who will revert to their own physician for follow-up. Thus the physician is a conduit through which most

From Fellowship Hall, Inc., P.O. Box 6929, Greensboro 27405.

victims, alcoholic and/or family, find help and remission, and continues to provide a consistent reference point after treatment.

Medical. Acute alcoholism provides progressive physical deterioration in all body systems, presenting symptomatic patterns that challenge the eager diagnostician: alcoholism masquerades as heart disease, diabetes, chronic high blood pressure, polyneuropathy, gastritis, insomnia, and arthritis, among others. Many, if not most, of these symptoms miraculously vanish in short order during treatment as the body begins to shrug off the effects of the systemic toxicity.

Most patients receive tapering doses of a tranquilizing compound to relieve the trauma of withdrawal. Other appropriate medications indicated by the admission physical examination (and/or as directed by the referring physician) are dispensed by a medical team as they monitor the patient's progress, effectively providing a formal record of diagnosis, treatment, and progress as well as a discharge summary and prognosis. Repeatedly throughout therapy, the patient is reminded of the responsibility he must assume for his own psychological/physical health. With rare exception, treatment programs stress a life free of any mood-changing chemicals.

Therapy. Coincident with and complementing the medical/physical efforts, teams of trained, professional counselors — usually armed with insight born of extensive personal experience — provide education and role model support as they interact with and monitor the patient in the restorative process. Individual and group therapy is a dynamic part of most treatment regimens. As the abstinent patients become physically restored, they find a strength of purpose in the commonality of their grief. Hope is rekindled and self-esteem reborn; life without sedation and dishonesty appears possible, even preferable. They learn to laugh with each other and at themselves as they inventory the motivations, values, and actions that are to carry them

into and through sobriety. *Fact:* stopping drinking is not enough.

Today's treatment appreciates the necessity and benefit of family involvement, providing a dynamic educational experience as basis for support, understanding, and change when treatment is complete and recovery begins. Family treatment is receiving expanding attention as some facilities commence formal inpatient family therapy.

Aftercare. Patients are counseled to appreciate alternatives for ancillary support (AA, Al-Anon, Alateen) or extended treatment. Personal contact is offered for the year following discharge. Hospital house organs, such as newsletters, alumni associations, and/or reunions are not uncommon.

Conclusions. Today's alcoholism treatment is professional and effective. It is part of a team effort that includes the intervening physician in a continuum of commitment to alleviate the major societal dysfunction and personal tragedy known as alcoholism.

A Note from the Editor:

I was skeptical of the success rate of 75%. I asked Dr. Jack Ewing, chairman of the North Carolina Medical Society Committee on Drug Abuse and Pharmacy for his opinion. He replied as follows:

"The claim of 75% success rate has been documented by some industrial corporations that have employee assistance programs. Identified alcoholic employees who have been sent to treatment programs such as the one offered by Fellowship Hall do seem to achieve success rates in terms of continued abstinence for several years at least in the region of 75%. This is one of the great advantages of having a considerate employer who is, nevertheless, willing to provide coercion.

"The doctor in general practice who cares for patients not enrolled in a corporate employee assistance program will not have a 75% success rate."

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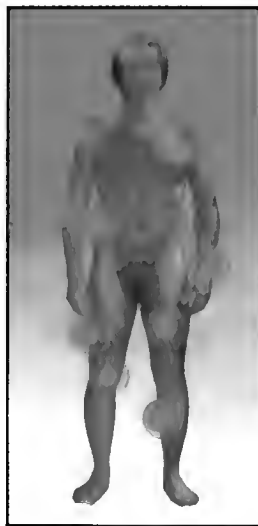
See important information on next page

Equagesic[®]

(meprobamate with aspirin) © Wyeth

Effective adjunct in short-term treatment of pain

accompanied by tension and/or anxiety in patients with musculoskeletal disorders.



When anxiety magnifies the perception of pain

*1-2 tablet dosage
3 or 4 times daily*

Equagesic[®] (meprobamate with aspirin) © Wyeth

(BRIEF SUMMARY)

DESCRIPTION Each tablet contains 200 mg meprobamate and 325 mg aspirin.

INDICATIONS

Adjunct in short-term treatment of pain accompanied by tension and/or anxiety in patients with musculoskeletal disease. Clinical trials demonstrated that in these situations relief of pain is somewhat greater than with aspirin alone. Effectiveness in long-term use (i.e., over 4 months) has not been assessed by systematic clinical studies. Physicians should periodically reassess usefulness of drug for individual patients.

CONTRAINDICATIONS

ASPIRIN: Allergic or idiosyncratic reactions to aspirin or related compounds.

MEPROBAMATE: Acute intermittent porphyria; allergic or idiosyncratic reactions to meprobamate or related compounds (e.g., carisoprodol, meprobamate, or carbamate).

WARNINGS

ASPIRIN: Use salicylates with extreme caution in patients with peptic ulcer, asthma, coagulation abnormalities, hypoprothrombemia, vitamin K deficiency, or those on anticoagulants. In rare instances, aspirin in persons allergic to salicylates may result in life-threatening allergic episodes.

MEPROBAMATE: DRUG DEPENDENCE. Physical and psychological dependence and abuse have occurred. Chronic intoxication from prolonged ingestion of usually greater than recommended doses is manifested by ataxia, slurred speech and vertigo. Therefore, carefully supervise dose and amount prescribed and avoid prolonged use, especially in alcoholics and others with known propensity for taking excessive quantities of drugs. Sudden withdrawal after prolonged and excessive use may precipitate recurrence of preexisting symptoms.

Example, e.g., anxiety, anorexia, or insomnia, or withdrawal reactions (e.g., vomiting, ataxia, tremors, muscle twitching, convulsions, seizures, hallucinations, and rarely, convulsive seizures). Such seizures are more likely in persons with CNS damage or preexisting or latent convulsive disorders. Onset of withdrawal symptoms occurs usually within 12 to 48 hours after discontinuation. Symptoms usually cease within next 12 to 48-hour period. When excessive dosage has continued for weeks or months, reduce dosage gradually over 1 to 2 weeks rather than stop abruptly. Alternatively, a short-acting barbiturate may be substituted then gradually withdrawn.

POTENTIALLY HAZARDOUS TASKS: Warn patients meprobamate may impair mental or physical abilities required for potentially hazardous tasks (e.g., driving or operating machinery).

ADDITIVE EFFECTS: Since CNS depressant effects of meprobamate and alcohol or meprobamate and other psychotropic drugs may be additive, exercise caution with patients taking more than one of these agents simultaneously.

USE IN PREGNANCY AND LACTATION An increased risk of congenital malformations associated with minor tranquilizers (meprobamate, chloralhydrate, and diazepam) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at time of institution of therapy should be considered. Advise patients if they become pregnant during therapy or intend to become pregnant to communicate with their physician about desirability of discontinuing the drug.

Meprobamate passes the placental barrier. It is present both in umbilical-cord blood at or near maternal plasma levels and in breast milk of lactating mothers at concentrations two to four times that of maternal plasma. When use of meprobamate is contemplated in breastfeeding patients, consider the drug a higher concentration in

breast milk as compared to maternal plasma levels.

USAGE IN CHILDREN: Keep preparations with aspirin out of reach of children. Equagesic[®] (meprobamate with aspirin) is not recommended for patients 12 years of age and under.

PRECAUTIONS

ASPIRIN: Salicylates antagonize uricosuric activity of probenecid and sulfinpyrazone. Salicylates are reported to enhance hypoglycemic effect of sulfonylurea antidiabetics.

MEPROBAMATE: Use lowest effective dose, particularly in elderly and/or debilitated to preclude over-sedation. Meprobamate is metabolized in the liver and excreted by the kidney. To avoid excess accumulation exercise caution in its use in patients with compromised liver or kidney function. Meprobamate occasionally may precipitate seizures in epileptic patients. It should be prescribed cautiously and in small quantities to patients with suicidal tendencies.

ADVERSE REACTIONS

ASPIRIN: May cause epigastric discomfort, nausea, and vomiting. Hypersensitivity reactions, including urticaria, angioneurotic edema, purpura, asthma, and anaphylaxis may rarely occur. Patients receiving large doses of salicylates may develop tinnitus.

MEPROBAMATE: CNS: Drowsiness, ataxia, dizziness, slurred speech, headache, vertigo, weakness, paresthesias, impairment of visual accommodation, euphoria, overstimulation, paradoxical excitement, fast EEG activity. GI: Nausea, vomiting, diarrhea.

CARDIOVASCULAR: Palpitation, tachycardia, various forms of arrhythmia, transient ECG changes, syncope, hypotensive crisis. **ALLERGIC OR IDIOSYNCRATIC:** Milder reactions are characterized by itchy urticarial or erythematous maculopapular rash, generalized or confined to the groin. Other reactions include leukopenia, acute nonthrombocytopenic purpura, patchy ecchymoses, eosinophilia, peripheral edema, adenopathy, fever, fixed drug eruption with cross reaction to propylthiouracil, and cross sensitivity between meprobamate, meprobamate and meprobamate carbamate. Rare, more severe hypersensitivity

reactions include hyperpyrexia, chills, angioneurotic edema, bronchospasm, oliguria, and anuria. Also, anaphylaxis, exfoliative dermatitis, stomatitis, and proctitis. Stevens-Johnson syndrome and bullous dermatitis have occurred.

HEMATOLOGIC (SEE ALSO "ALLERGIC OR IDIOSYNCRATIC") Agranulocytosis, aplastic anemia have been reported, although no causal relationship has been established, and thrombocytopenic purpura.

OTHER: Exacerbation of porphyric symptoms. **DOSE AND ADMINISTRATION:** Usual dose is one or two tablets, 3 to 4 times daily as needed for relief of pain when tension or anxiety is present. Not recommended for patients 12 years of age and under.

OVERDOSEAGE

Treatment is essentially symptomatic and supportive. Any drug remaining in the stomach should be removed. Induction of vomiting or gastric lavage may be indicated. Activated charcoal may reduce absorption of both aspirin and meprobamate. Aspirin overdose produces usual symptoms and signs of salicylate intoxication. Observation and treatment should include management of hyperthermia, specific parenteral electrolyte therapy for ketonacidosis and dehydration, watching for evidence of hemorrhagic manifestations due to hypoprothrombemia which, if it occurs, usually requires whole blood transfusions. Suicidal attempts with meprobamate have resulted in drowsiness, lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse. Some suicidal attempts have been fatal.

The following data, reported in the literature and from other sources, are not expected to correlate with each case (considering factors such as individual susceptibility and length of time from ingestion to treatment), but represent usual ranges reported. Acute severe overdose (meprobamate alone): Death has been reported with ingestion of as little as 12 grams meprobamate and survival with as much as 40 grams.

BLOOD LEVELS

0.5-2.0 mg percent represents usual therapeutic range of meprobamate after therapeutic

doses. The level may occasionally be as high as 3.0 mg percent.

3-10 mg percent usually corresponds to findings of mild-to-moderate symptoms of overdose, such as stupor or light coma.

At levels greater than 20 mg percent, more fatalities than survivors can be expected.

Acute combined overdose (meprobamate with other psychotropic drugs or alcohol). Since effects can be additive, history of ingestion of a low dose of meprobamate plus any of these compounds (or of a relatively low blood or tissue level) cannot be used as a prognostic indicator.

In cases of excessive doses, sleep ensues rapidly and blood pressure, pulse, and respiratory rates are reduced to basal levels. Any drug remaining in stomach should be removed and symptomatic treatment given. Should respiration or blood pressure become compromised, respiratory assistance, CNS stimulants, and pressor agents should be administered cautiously as indicated. Diuresis, osmotic (mannitol) diuresis, pentothal dialysis, and hemodialysis have been used successfully in removing both aspirin and meprobamate. Alkalinization of the urine increases excretion of salicylates. Careful monitoring of urinary output is necessary, and caution should be taken to avoid overhydration. Relapse and death after initial recovery have been attributed to incomplete gastric emptying and delayed absorption.

HOW SUPPLIED

Scored tablets, bottles of 100. Redipac[®] strip pack, 25's. Redipac[®] unit dose 100's, individually wrapped.

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Strongyloidiasis at North Carolina Memorial Hospital

Richard A. Davidson

IN two previous articles I have described case series of patients with ascariasis and giardiasis. Both of these infections involve young, reasonably healthy individuals, even in series collected in a referral hospital population; both may cause discomfort (especially giardiasis), but rarely cause serious illness. *Strongyloides stercoralis* is a nematode which affects an older population and, if untreated, may cause fatalities.

Life Cycle and Symptomatology

Strongyloides stercoralis is unusual among human parasites in that it is not an obligate parasite; it has a free living life cycle, which enables it to reproduce and survive in the absence of humans. The organism prefers moist, sandy soil as is frequently found in the eastern half of North Carolina. One of its larval stages, the filariform larva, has the capability of penetrating human skin, and this is how the infection is obtained. The microscopic larvae penetrate the skin of the foot and ankle most frequently, and may cause a pruritic erythematous rash, especially in persons who have been previously infected. The larvae travel via the circulatory system to the lungs, where they mature in alveoli. During this portion of the life cycle, the patient may develop wheezing, coughing, a hemorrhagic pneumonia, or no symptoms at all; most patients will develop eosinophilia during this maturation phase.

Breaking out of the alveoli, the adolescent worms are coughed up and swallowed, and reside and mature in the duodenum or jejunum. Another unusual aspect of the life cycle is that the parasitic stage is parthenogenetic; male adult worms are not tissue parasites, and are passed in the stool. The female adults, 2 mm long, live in the crypts of the small intestine, where they lay eggs in the mucosa. These eggs hatch, and the rhabditiform larvae that emerge are passed in the stool. These larvae are the diagnostic stage that is usually seen in the parasitology laboratory. Symptoms found in chronic infection are usually mild, and include intermittent abdominal pain, bloating, and diarrhea.

Difficulties arise when the rhabditiform larva, which cannot penetrate tissue, metamorphoses within the body to the filariform larva, which readily penetrates the gut wall, carrying enteric bacteria with it; this causes polymicrobial sepsis and the so-called hyperinfection syndrome, which may have an 86% mortality.^{1, 2} Filariform larvae may be found in the sputum, urine, or central nervous system in addition to the stool. The hyperinfection syndrome is clear-

ly associated with conditions that cause defective cell-mediated immunity, such as corticosteroid usage, hematologic malignancies, protein-calorie malnutrition, and leprosy;³ it represents a medical emergency and requires intensive and immediate therapy. Some authors recommend evaluating all patients who are to be immunosuppressed prior to their therapy; this may be especially worthwhile in patients who have undergone renal transplants, a number of whom have died from hyperinfection.⁴⁻⁶

Diagnosis

The diagnosis is made by finding larval forms, usually the rhabditiform stage, in the stool. Three stool specimens will diagnose between 80 and 92% of infected patients. Unfortunately a percentage of patients will have larvae demonstrable in duodenal aspirates in spite of many negative stools; those patients in whom there is a strong clinical suspicion of strongyloidiasis but multiple stools are negative should undergo some evaluation of duodenal material. The Enterotest, an encapsulated string which is swallowed and then retrieved, is relatively simple to use, only mildly uncomfortable, and is as sensitive as three stool exams.⁷ Other methods of obtaining duodenal material, such as endoscopy and small bowel biopsy, are equally effective. Approximately 95% of infected patients will have over 5% eosinophils on differential white blood cell count. No reliable serum tests for diagnostic purposes are yet available.

Treatment

Thiabendazole is definitively the drug of choice in this infection, in a dose of 25 mg/kg/day, two divided doses per day on two successive days. This course of treatment may be repeated in 7 days, especially in immunocompromised individuals; this regimen will successfully treat over 96% of infected persons.⁸ Careful followup to ensure a parasitic cure is highly recommended.

Case History

FB, a 59-year-old man from Roanoke Rapids, was admitted to NCMH for evaluation of recent symptoms of cord compression. He had a fifteen-year history of seropositive rheumatoid arthritis and active cervical spine disease had led to progressive weakness and loss of function in his lower extremities. He had been treated with prednisone, 10 mg every other day, for 4 years prior to admission. He denied any symptoms referable to the gastrointestinal tract, except for occasional indigestion after eating spicy foods. He specifically denied abdominal pain, bloating, nausea,

From the Department of Medicine, University of North Carolina, Chapel Hill 27514.

or vomiting. He underwent decompressive surgery by the neurosurgery service and was transferred to the rehabilitation service for the remainder of his admission. He was begun on penicillamine, and at that time was noted to have 7% eosinophils on differential white blood cell count. This was ascribed to his penicillamine, but it persisted after the drug was discontinued. Two stool examinations were negative, but an Enterotest revealed the presence of rhabditiform larvae of *Strongyloides stercoralis*. He was treated with two courses of thiabendazole, and at a followup visit 3 months later had no eosinophilia and stools were negative for ova or parasites.

Case Series

The records of all patients with proven strongyloidiasis at the North Carolina Memorial Hospital for the ten-year time period between 1971 and 1981 were reviewed. Forty-five patients were diagnosed; only forty charts were available for review. The forty patients had a mean age of 47.9 years; 82% were male and 67% were white. The mean eosinophil count was 15.3%; 37 of the 40 (92%) had greater than 5% eosinophils. Twelve of the patients were recent immigrants to the United States from Viet Nam, Cambodia, Laos, Africa, Haiti, and Puerto Rico. Sixty percent of the patients had gastrointestinal complaints: 30% had diarrhea, 22% abdominal pain, and 10% bloating. Thirty percent had evidence of a skin rash. Fifty-five percent had stools sent to the lab because of eosinophilia alone, 17.5% because of gastrointestinal symptoms, 15% because of both, and 12.5% for other reasons; thus, 70% of the patients could have been diagnosed only on the basis of eosinophilia. Coexisting diseases found in the forty patients are shown in table 1.

Table 1
Major Coexisting Diseases in Forty Patients With Strongyloidiasis

Peptic ulcer disease (12)
Multiple parasites (8)
Hematologic malignancy (5; 2 Hodgkins, 2 CLL, 1 ALL)
Non-hematologic malignancy (5; adrenal, hepatoma, breast, prostate, lung)
Severe coronary heart disease (3)
Rheumatoid arthritis (2)
Tuberculosis, histoplasmosis, disseminated granulomatous disease, hemophilia, chronic renal failure, ITP, and bronchiectasis each occurred once.

While no patients had documented hyperinfection syndrome, one ten-year-old child with acute lymphocytic leukemia died outside the hospital of sepsis at a time when his leukemia was in remission. He was taking prednisone, and had been diagnosed as having strongyloidiasis 3 months earlier. He was never treated for the infection. A postmortem examination was not done.

A control population was collected and compared with these cases. The results, which will be published elsewhere,⁹ demonstrated statistically significant associations with the white race, male sex, corticosteroid usage, hematologic malignancy, and prior gastric surgery.

This case series is similar to others in the literature,^{10, 11} and suggests that the average patient with strongyloidiasis is a white male, approximately 50 years of age, with an average eosinophil count of around 15%. Two-thirds have gastrointestinal complaints, usually intermittent in nature, including diarrhea, abdominal pain, bloating, nausea, and vomiting. Over half have serious underlying chronic illness. Patients with these characteristics should be evaluated for the possibility of strongyloidiasis, including duodenal evaluation when stools are negative; those patients who are immunocompromised should be vigorously investigated, as they are at great risk if untreated infection is present.

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Management of Nose Bleed

Patrick D. Kenan, M.D.

FEW of us go through life without experiencing minor nose bleed from time to time. For some, this can be a serious and even life-threatening event, particularly when associated with blood dyscrasias, severe hypertension, liver disease, and cancer. Fortunately, most problems of nose bleed are more of a nuisance than a threat and lend themselves to relatively simple principles of home or office management.

The commoner forms of nose bleed are related to venous bleeding from the anterior septum which can be controlled by external compression of the alar rims, followed by application of a cotton pack saturated with any topical vasoconstrictor and placed within one or both nasal vestibules. A bilateral anterior pack sandwiches the septum and usually results in more effective tamponade of the bleeding site than a unilaterally applied pack. This is a technique that patients prone to frequent recurrent nose bleed can be taught to do on their own whenever the need arises. All that is required is to have small cotton balls and a bottle of vasoconstrictor nose drops available and control can be achieved almost immediately. The packs can usually be removed within an hour or so.

When confronted in an office setting with the typical anterior nose bleed, the physician should apply some form of tamponade first, and consider some form of cauterization if the bleeding site can be accurately identified. Silver nitrate or even electrocoagulation is useful for this purpose, provided some form of topical or local anesthetic is applied first. In effect, this form of "spot welding" can achieve immediate and often lasting control, though it may be necessary to recauterize in ten to fourteen days before complete control and healing are achieved. This is a technique apropos to small children as well as the elderly, both groups being at high risk for nose bleed.

Oftentimes the cause of bleeding relates to dryness and cracking of the nasal mucosa, either from the natural atrophy that accompanies aging or from exposure to dry heat. These cracks or fissures often occur directly over a point of artilaginous or bony deflection where the mucosa is stretched or easily traumatized. With such findings present in association with repeated bleeding tendencies, septal surgery to relieve the points of deflection may be curative.

More severe forms of bleeding may justify the application of nasal packs for several days at a time. One of the more comfortable anterior packs is made from folded or rolled Telfa, coated with an antibiotic ointment such as bacitracin. This method of packing is far easier than applying long strips, and is especially appropriate in a clinical

setting of limited equipment or illumination. A relatively inexperienced provider can apply a folded piece of Telfa as a tamponade, whereas it takes experience and equipment to apply strips of packing material effectively.

It should be emphasized that as a general rule, bilateral packing is more effective and indeed more comfortable to the patient than unilateral packing, as the former maintains equal and opposite pressure against the septum, sandwiching it between packs, whereas the latter is often inclined to cause an uncomfortable displacement of the cartilaginous septum to the opposite side.

More severe forms of epistaxis are usually associated with posterior or nasopharyngeal bleeding from branches of the sphenopalatine artery. This type of bleeding is not likely to respond to anterior packs unless they are vigorously applied against the nasopharyngeal mucosa. A posterior pack is usually indicated in this situation. The classical posterior pack is a complicated arrangement of strings tied around a rolled sponge. It is placed into the nasopharynx in a retrograde manner by first introducing a small catheter through the nostril and out the mouth, tying a retraction string onto the oral end of the catheter, and then retracting the catheter, thus pulling the pack into the nasopharynx. There is usually a drawstring left in place in the pharynx, or out the mouth and taped to the cheek. The drawstring extracts the pack at the appropriate time two or three days after its application. The posterior pack is usually secured in place by tying the nasal string over a rolled sponge at the nostril, after first applying a conventional anterior pack once the posterior pack is in place.

Placement of classical posterior packs is unpleasant to the patient and usually necessitates prior application of topical vasoconstrictors and anesthesia to the nose and throat. The packs are quite uncomfortable during the time they are in place, and usually justify the administration of sedatives or narcotic containing analgesics. Worse yet, upon removal of large bulky packs, rebleeding often occurs, necessitating repacking, which only adds to the existing misery.

A simpler and less traumatic form of posterior packing, though not always so effective, is the use of nasal or nasopharyngeal balloons. The simplest is a Foley catheter with a 15 cc inflated balloon which is inflated with air or saline. The catheter is inserted into the nasopharynx, antegrade through the nostril, the balloon is inflated, and then the catheter is pulled gently against the posterior choana and taped in place at the cheek. The size of the Foley catheter usually precludes the simultaneous use of anterior packing.

Other commercially available balloon catheters are specifically made for posterior nasal tamponade, and some are

from the Department of Surgery, Duke University Medical Center, Durham 27710.

embellished with an additional anterior balloon which both serves as an anterior pack and secures the apparatus at the nostril. Unfortunately, these balloons have a high failure rate with rupture of the balloon being the most common fault.

Adjunctive measures in the office or home management of nose bleed include use of cold substances for their vasoconstrictor effects. External ice packs, ice chips p.o., ice water gargles are all useful measures. Conversely, ingestion of excessively hot food or drink with its attendant vasodilator effects should be discouraged. Head elevation to reduce venous pressure in nasal membranes is naturally desirable. Avoidance of heavy exertion or straining at stool secondary to constipation are to be avoided.

On removal of packs, vigorous nose blowing is to be avoided but good humidity in the inspired air, good nasal hygiene through normal saline douching, and removal of crusts or clots by the rhinologist are useful management techniques.

Salicylates and anticoagulants are counterproductive to controlling nose bleed and should be avoided, interrupted, or at least reduced in the acute management of nose bleed or in the post packing phase. Vitamin K administration may be indicated as well as the giving of fresh whole blood or plasma.

Certain severe forms of epistaxis simply will not respond to conventional packing and may require surgical ligation

of the primary blood supply to the nose. This may be accomplished by anterior and posterior ethmoid artery ligation through a medial superior orbital approach, or through transantral ligation of the internal maxillary arteries which supply the sphenopalatine vessels. There is probably no role for external carotid artery ligation, though this was a popular approach in the management of severe epistaxis twenty or more years ago. There is an important place for embolization of the internal maxillary artery which of course requires vascular radiology resources with selective catheterization of the internal maxillary artery via the external carotid artery. Surgical and embolization methods are best accomplished in the setting of a hospital or medical center, often with input from the internist or hematologist in the management of severe hypertension, coagulopathy, liver failure, or blood dyscrasia.

Preventive measures in the patient prone to nose bleed include careful regulation and management of underlying causes such as hypertension, alcoholism, etc., avoidance of nasal trauma associated with overly forceful nose blowing, nose picking, etc., and the maintenance of good hydration of the nasal membranes and good humidity in the inspired air. Therefore, a good oral fluid intake, use of bedside vaporizers or room humidifiers, saline nasal douching, and topical application of water-soluble lubricants such as Vaseline, can be useful prophylactic measures in the prevention of nose bleed.

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Breast Reconstruction Following Mastectomy

G. Georgiade, N. Georgiade, R. Riefkohl, D. Serafin and W. Barwick

AN evaluation of approximately six hundred patients who have undergone breast reconstruction at the Duke University Medical Center reveals a number of interesting findings.

Reconstruction of the breast following mastectomy has become an accepted procedure and is being demanded by more and more patients as they become aware of the option of reconstruction. In the more than 600 patients whom we have reconstructed there has been no demonstrable evidence of any effect on the course of the initial disease. The patients are generally very well satisfied with the results and delighted with the fact that their ability to wear all types of clothing and to participate in active sports has been enhanced because they no longer have to wear an external prosthesis. Psychologically many have expressed the opinion that they feel "whole" once again, which provides them with an emotional uplift.

In approximately 75% of patients who have had a mastectomy, the breast mound can be reconstructed by the simpler technique of placing a Silastic implant in the subpectoral subseratus muscle position in order to create a breast mound. This procedure usually necessitates a short one or two day hospitalization, and on occasion is carried

out in our outpatient Surgicenter. Over 125 selected patients in our series elected to have the first stage of their reconstruction carried out on an "immediate" basis at the time the ablative surgery was performed. Utilizing this technique saves the patient an operative procedure with no compromise in the original ablative surgery. Approximately four to six months later the final matching of the breast mounds can often be accomplished if there is not too marked a dissimilarity in the breast mounds and no additional surgery such as a subcutaneous mastectomy is performed on the opposite breast (figures 1-5).

In our initial series of patients who had breast reconstruction there were many patients who had undergone the Halstead radical mastectomy. Because of the difficulty in reconstructing the surgical defect created by removal of the pectoral muscle during the initial radical procedure, it was difficult to obtain an adequate aesthetic result. The evolution of the newer techniques involving transfer of musculocutaneous latissimus dorsi flaps (figure 6) and more recently rectus abdominus flaps (figures 7 and 8) to the chest area has allowed us to reconstruct the entire defect. Occasionally it has been necessary for us to reconstruct the chest defect utilizing a latissimus dorsi musculocutaneous flap from the unoperated side transferring this as a "free flap" using microsurgical techniques (figure 9).

The missing nipple-areola complex is constructed at the final stage. At the present time the areola is constructed

from the Division of Plastic, Maxillofacial & Reconstructive Surgery, Duke University School of Medicine, Durham 27710.

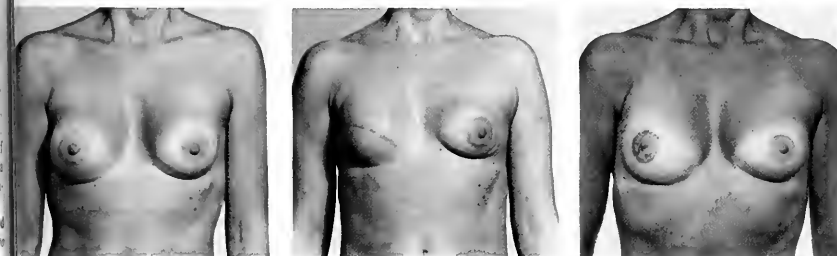


Figure 1. Left: Preoperative view of a 40-year-old patient who underwent a right modified radical mastectomy for florid intraductal papillomatosis with immediate insertion of a Silastic prosthesis. Middle: Six months postoperatively. Right: Postoperative front view of the patient after seven years. Nipple was reconstructed by "nipple sharing."

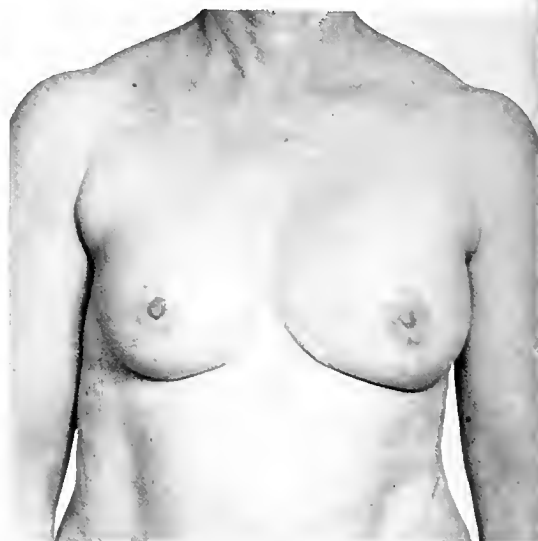


Figure 2. Left: Preoperative front view of a 48-year-old patient who had intraductal carcinoma in the upper outer quadrant right breast. Right: Three years postoperatively. She had a right modified radical mastectomy, "immediate" reconstruction and left subcutaneous mastectomy with implant.



Figure 3. Left: A nine month postoperative view of a 31-year-old patient who had had a left modified radical mastectomy for adenocarcinoma with immediate insertion of a Silastic prosthesis and a right subcutaneous mastectomy with insertion of a Silastic prosthesis. Right: A postoperative view three months later following reconstruction of the nipple by nipple sharing and a groin graft for construction of the areola.

using a full thickness skin graft from the groin which offers the best color correlation with the normal areola. The nipple is constructed either using a local flap, which is later

tattooed for color coordination with the opposite nipple, or removing a portion of the opposite nipple and nipple sharing.

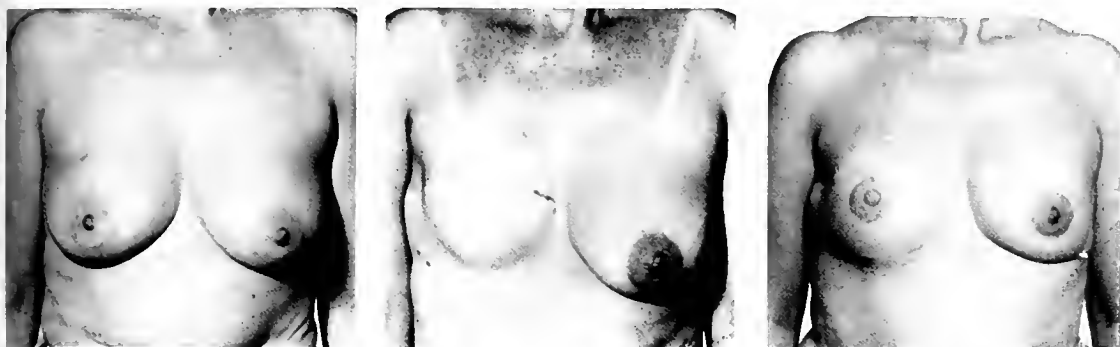


Figure 4. Left: Preoperative front view of a 41-year-old patient with carcinoma of the right breast. Middle: She had a modified radical mastectomy for intraductal carcinoma with immediate insertion of a Silastic prosthesis; a four month postoperative front view. Right: A one year postoperative reconstruction front view of the same patient. A subcutaneous mastectomy was carried out on the left breast.

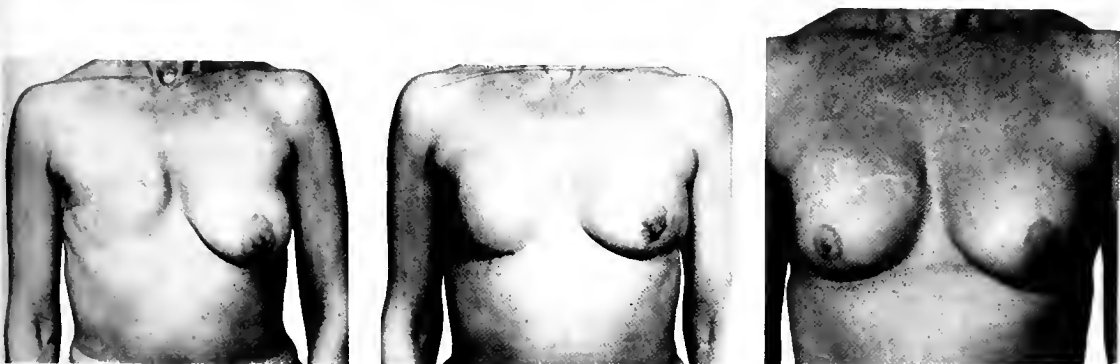


Figure 5. Left: Preoperative front view of a 46-year-old patient who had a right modified radical mastectomy a year previously for tubular carcinoma of the breast. Middle: A seven month postoperative front view of the same patient following insertion of a Silastic prosthesis in the right breast mound and a subcutaneous mastectomy of the left breast with insertion of a Silastic prosthesis. Right: A postoperative front view of the same patient seven years following reconstruction.

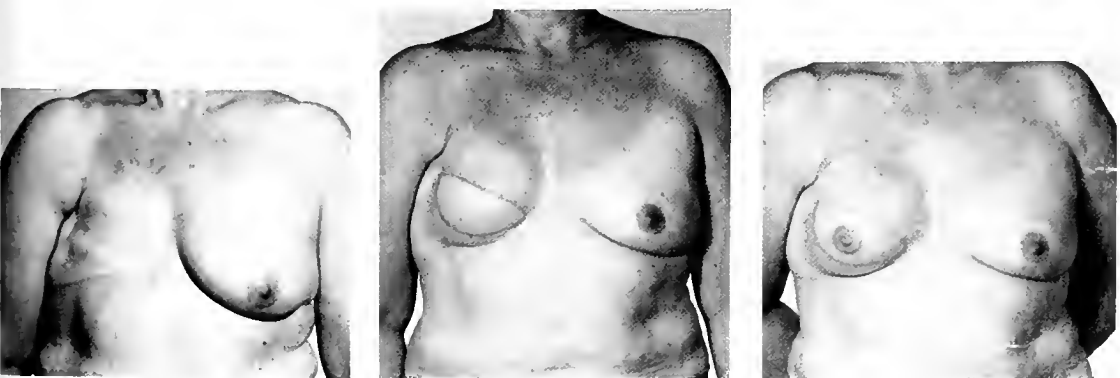


Figure 6. Left: A preoperative front view of a 49-year-old patient who had a modified radical mastectomy performed four years previously for infiltrating ductal carcinoma followed by cobalt treatment. Middle: Five months following transfer of a right latissimus dorsi pedicle flap and a left subcutaneous mastectomy with insertion of a Silastic prosthesis. Right: Ten months following initial surgery and reconstruction with local nipple flap and a groin full thickness skin graft for areola.

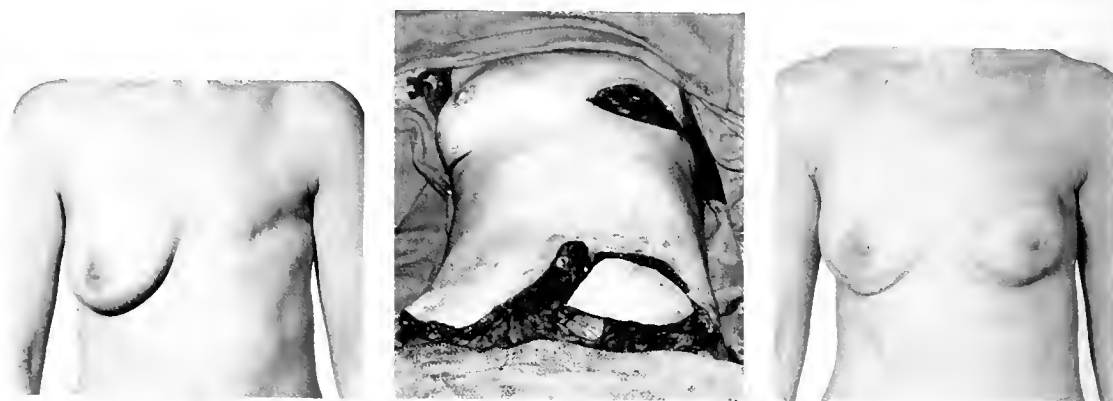


Figure 7. Left: 35-year-old patient with resection of pectoral muscle and modified radical mastectomy. Middle: Creation of a large rectus abdominus musculocutaneous flap and preparation of breast site for transfer. Right: Postoperative appearance of one stage breast reconstruction, "tummy tuck" and later creation of nipple and areola.



Figure 8. Above left: A preoperative front view of a 53-year-old patient who had a left radical mastectomy seventeen years previously for infiltrating ductal carcinoma. Above right: The large abdominal rectus myocutaneous flap necessary to construct the large chest and axillary deformity is shown. (Opposite page.) Top left: Transfer of the myocutaneous flap from the abdominal area. Top right: A seven-month postoperative view of the same patient following reconstruction of left chest defect and right subcutaneous mastectomy.

Summary

Breast reconstruction following mastectomy for carcinoma can be initiated immediately following the ablative surgery and during the same operative procedure. If reconstructive breast surgery is deferred for reasons such as

chemotherapy or desire of the the patient, the initial reconstructive procedure can be instituted at any time by one of the techniques previously described.

Evaluation of our patients in this large series has failed to demonstrate that reconstructive surgery in any way affected the course of the patient's initial disease.

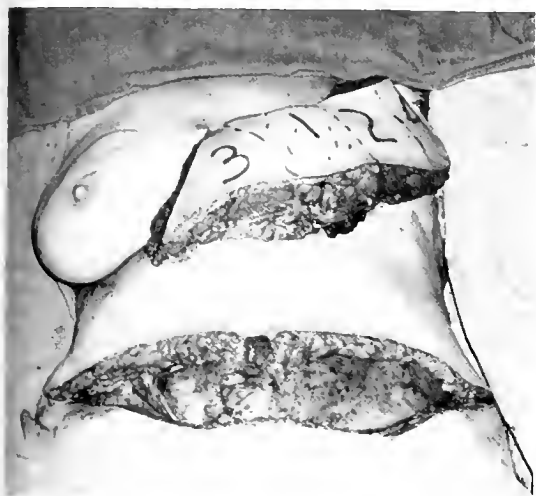


Figure 9. Left: Preoperative front view of a 45-year-old patient who had a left radical mastectomy with right split thickness skin graft two years previously. Right: A 2½ year postoperative front view. The left breast was reconstructed utilizing a latissimus dorsi musculocutaneous free flap to resurface the chest area. Following this a Silastic prosthesis was placed in the subpectoral subseratus position. A left subcutaneous mastectomy was performed with simultaneous insertion of a Silastic prosthesis. The nipple was reconstructed by nipple sharing and the areola by utilizing a full thickness groin graft.

Delegate Report From the AMA Meeting

John Glasson, M.D.

THE American Medical Association House of Delegates, meeting in Los Angeles between December 1 and 7, 1983, considered some 60 reports from the Board of Trustees and Councils plus 128 resolutions submitted by state delegations, individual delegates, medical specialty societies, and section councils of the American Medical Association.

The delegates received, in advance, approximately 50 resolutions and had submitted to them at the meeting an additional 78 resolutions which had been forwarded predominantly from the section on hospital medical staff, resident section and student section which met in Los Angeles immediately prior to the House of Delegates meeting.

The Hospital Medical Staff Section of the American Medical Association, meeting for two days immediately prior to the opening of the AMA House of Delegates, was again noteworthy as a breath of fresh air at the AMA meeting. In this section, some 700 physicians who are AMA members and who have positions of responsibility on hospital medical staffs throughout the nation, met in a formal House of Delegates format, now known facetiously in the AMA as "The Big House." Their deliberations were concerned primarily with three big issues.

First, consideration of the current changes in reimbursement of hospital services now being implemented by the Health Care Financing Administration. The hospital medical staff delegation from New Jersey was particularly concerned about the relationship between physicians and hospitals. They introduced several resolutions aimed at having the AMA assure by policy that aberrant physician profiles of practice as they affect economics should not be construed as adequate cause for withdrawal of privileges to practice in our hospitals.

Their second concern was that hospital medical staffs be given maximum responsibility for control of medical practice, even though ultimate control was determined to rest with hospital Boards of Trustees.

The third big question considered was the matter of the rewriting of the medical staff section of the Joint Commission on Accreditation Standards for Hospitals. Even though the hospital medical staff section voted to go back to the drawing board and start over, the ultimate action by the AMA House of Delegates favored a final resolution introduced by the Alabama state delegation. The provisions of this resolution became the basis for an amendment introduced by the AMA members of the Joint Commission on Accreditation of Hospitals so that the section involved reads as follows:

1. Individuals granted the privilege to admit patients to inpatient services are members of the medical staff.

Individuals are granted the privilege to admit patients to inpatient services in accordance with state law and criteria for standards of medical care established by the individual medical staff. When nonphysician members of the medical staff are granted privileges to admit such patients, provision is made for prompt medical evaluation by a qualified physician for all such patients. This requirement for prompt medical evaluation by a qualified physician does not apply to qualified oral surgeons who have been granted the clinical privileges to perform a history and physical examination.

The wording for the Medical Staff Section created more correspondence between members of the N.C. Medical Society and its AMA delegates than any other issue, and we of the delegation appreciated hearing from our membership on this and other matters prior to the meeting.

The House of Delegates gave final approval to changes in the Constitution and Bylaws providing the addition of a resident physician to the AMA Board of Trustees as a voting member and the addition of a medical student to the AMA Board of Trustees as an ex-officio non-voting member. We in North Carolina are particularly proud of the fact that two North Carolina medical students, Al Osbahr and Keith McManus, are among the three medical students from the entire U.S. who were nominated as possible student members of the Board of Trustees.

The House of Delegates, in considering the matter of indemnity payments provided by insurance policies, rather than payments under the usual customary or reasonable concept which has for so long been the official policy of the AMA, reported the concept of multiple availability of types of payment depending on individual situations rather than the total abandonment of the UCR concept.

Also accepted, and of considerable general interest, was the Council on Medical Service report on standards for schedules of coverage provided employees under self-insurance programs.

A report by the Council on Scientific Affairs on recommendations for screening for breast cancer produced considerable controversy and discussion on the floor of the House but was eventually passed by a small margin. It is a rather thorough discussion which continues to support mammography as the best screening method available but goes into useful specifics regarding the value of self-examination for breast cancer.

Also very challenging were the reports and recommendations of the Council on Scientific Affairs for Hospitals as regards control of smoking in hospitals and a related resolution calling for the American Medical Association to promote the development of a smoke-free AMA staff by the year 2000.

In other actions, the House received an excellent report from the Council on Scientific Affairs on exercise for the elderly and from the Council on Medical Education on the availability of residency positions in the first post graduate year following medical school, indicating that available positions are now adequate at this level of training.

The House received and approved a report opposing the concept of surrogate motherhood and, in a timely action, also passed a resolution opposing the federal role in the so-called "Baby Doe" cases and supporting the right of parents and physicians locally to make final decisions in the case of severely handicapped infants in their medical management.

In an overwhelming vote by its House of Delegates, the American Medical Association has called for a narrowing of the use of the insanity defense in criminal trials.

The report calls for replacement of the conventional insanity defense with statutes that would permit a defendant to be acquitted on insanity grounds only if the mental disease prevented him or her from committing the criminal act with the requisite state of mind, or mens rea.

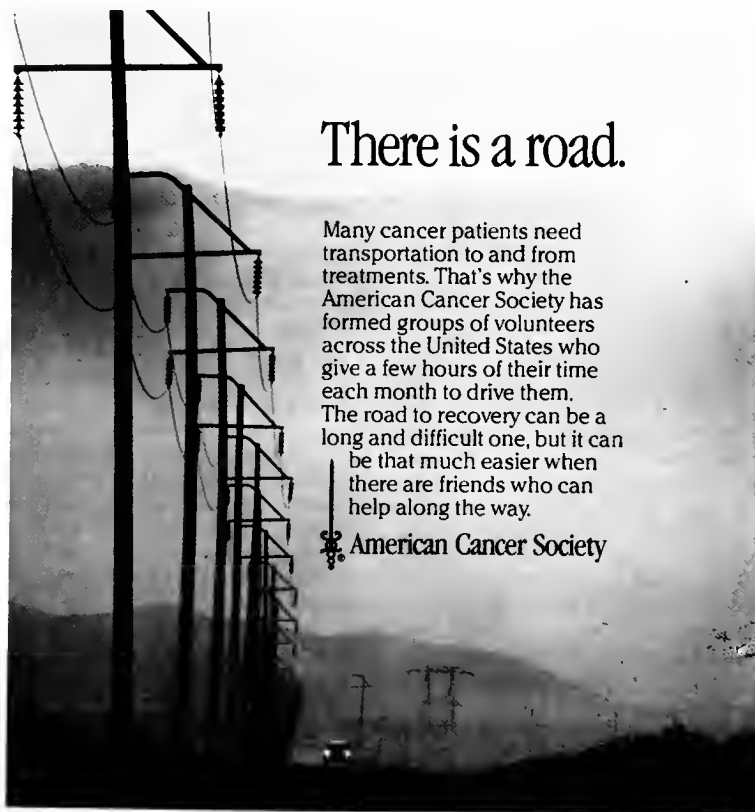
Currently, most jurisdictions use the more conventional

definition of insanity, which permits criminal defendants to plead insanity and be acquitted by providing evidence that at the time of the crime, the defendant lacked the capacity either to appreciate the criminality of his conduct or to conform his conduct to the requirement of the law.

The AMA is the first national organization to have adopted a policy calling for the narrowing of the insanity defense.


In addition to adopting the report, the delegates also agreed to continue collaborative efforts with the psychiatric and bar associations in an attempt to achieve a common policy position concerning the insanity defense.

The members of the Delegation particularly appreciated many comments received following the report on indemnity insurance payments published in the *North Carolina Medical Journal* (September 1983, page 577), as well as letters regarding other matters to be considered by the American Medical Association House of Delegates. We encourage more of this from all our North Carolina Medical Society members when future issues in medical care come to their attention.



There is a road.

Many cancer patients need transportation to and from treatments. That's why the American Cancer Society has formed groups of volunteers across the United States who give a few hours of their time each month to drive them. The road to recovery can be a long and difficult one, but it can be that much easier when there are friends who can help along the way.

 American Cancer Society

This space contributed as a public service.

James Bell Bullitt, M.D., 1874-1964: A University of North Carolina Medical Giant

John Borden Graham, M.D.

The University of North Carolina recently dedicated the Preclinical Educational Building on the Chapel Hill campus to Kenneth Brinkhous and to James Bell Bullitt. Dr. Bullitt was one of the four great leaders of the School of Medicine in the first half of the twentieth century, the others being Isaac Hall Manning, Professor of Physiology; Charles Staples Mangum, Professor of Anatomy; and William de Berniere MacNider, Professor of Pharmacology. Those four men charted the course and fought hard for the four-year medical school. Dr. Bullitt felt so strongly about this that he created an endowment fund to help support a four-year school and placed his own funds into it.

Dr. John Graham, one of his students, writes down some of his memories of the North Carolina giant.
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I want to share with the readers of the *North Carolina Medical Journal* my thoughts of Dr. James Bell Bullitt. I was very fond of him, and he had an important influence on my life. In fact he served in *loco parentis* to me as I shall recount, although I doubt that he was aware of it.

Dr. Bullitt was born in Louisville, Kentucky in January 1874, 110 years ago, and lived to the age of 90, dying in March 1964. He was Professor of Pathology here from 1913-46 and served an additional 18 years as emeritus elder statesman, counselor, and friend of the Department and School. He came to his office almost daily until his final illness began two years before his death.

Dr. Bullitt belonged to a large family which has played an important role in the affairs of the state of Kentucky and of our nation. One of his great-grandfathers was Louis Marshall, the younger brother of John Marshall, the great Chief Justice of our Supreme Court. Justly or not, Louis Marshall, who was studying medicine in Paris during the French Revolution, was imprisoned for several years for "revolutionary activities." After his release Dr. Marshall practiced medicine in Kentucky and was later president of both Transylvania University and Washington College, now Washington and Lee University. Dr. Bullitt's brother, William M. Bullitt, was for many years an important figure in Kentucky politics and served as Solicitor General of the United States in the Taft administration. A cousin, William C. Bullitt, was the first American Ambassador to the Soviet Union in the late 1930s.

After his early education at Rugby Preparatory School in Louisville, Dr. Bullitt enrolled at Washington and Lee, then at Charlottesville in Virginia. His education occurred at the time when Cardinal Newman's "Idea of the University" was the American ideal, graduate education of the German type having only just been introduced at Johns Hopkins and Chicago. Newman's dictum, *mens sana in corpore sano*, was Dr. Bullitt's creed. In modern idiom, he

was a man of high intelligence who tried to remain physically fit all his life.

Another influence which must have shaped Dr. Bullitt's outlook was the four years spent at Washington and Lee not long after General Lee's presidency. In the South at that time Lee's ideals — real and imaginary — were regarded as the hallmark of a gentleman. These included courtesy, kindness, thoughtfulness, and an elevated view of womanhood which seems very odd to us today. (Another W & L graduate, Tom Wolfe, has referred to this view of women as the "Myth of the Ice Goddess.") Generations of medical students referred to Dr. Bullitt affectionately and respectfully as "Gentleman Jim."

He was a life-long athlete. He played football at Washington and Lee and I think I remember his telling me that he was also on the football team at Virginia while a medical student. Although he played line-backer and full-back, he was not a large man. But American football was a different sport at the turn of the century, more like English rugby than armored warfare. My father, for instance, weighed only 118 pounds when he was All State quarterback at Davidson in 1910. Dr. Bullitt's appearance was that of an athlete. He walked with a firm step and stood straight as a ramrod as long as I knew him.

I first encountered Dr. Bullitt as a second-year medical student in 1939 when I was 21 and he was 65. My class was the first to study pathology in the "new" medical school building — now MacNider Hall. On the first day of class we were met by a dignified and erect gentleman who appeared to be of middle age and who gave us detailed instructions on how to conduct ourselves in his course. The equipment in his new teaching laboratory included a new type of stool whose height could be adjusted and which swiveled 360 degrees. Wishing to be certain that everyone understood how to use it, Dr. Bullitt placed one atop the bench behind which he was to lecture, hopped up on the bench top, and spun himself around. We were dumbfounded, astonished both at the agility of this elderly gentleman and at the dignity with which he conducted himself

From the Department of Pathology, University of North Carolina, Chapel Hill 27514



Dr. Bullitt as captain of the football team at Washington and Lee University in 1894.

He always possessed complete aplomb, and I never once observed him to show a trace of self-consciousness.

Ten or fifteen years later, when Dr. Bullitt was now retired and must have been in his late 70s, I remember a conversation in the hall of MacNider with him and another person, possibly George Penick. We were discussing the importance of physical fitness. Dr. Bullitt insisted that it was a life-long matter and made his point by plopping down on the floor, salt-and-pepper grey suit and all, and proceeded to do five pushups. I am sure he would have done 25 had his astonished colleagues challenged him.

In conversation Dr. Bullitt spoke clearly, steadily, and at sufficient length to leave no uncertainty about his meaning. He joked about his loquacity and told a story on himself about a lengthy examination in college. Essay questions were normative in the 1890s, and Washington and Lee permitted unlimited time to respond. He wrote for seven hours on an examination and made a good grade, but his instructor requested that he come by for an interview. It consisted of a series of questions and answers.

"Are you from Kentucky?" "Yes."

"Are the women beautiful there?" "They seem to be."

"Are the race horses fast?" "They are said to be."

"Is the whiskey good?" "I suppose it is."

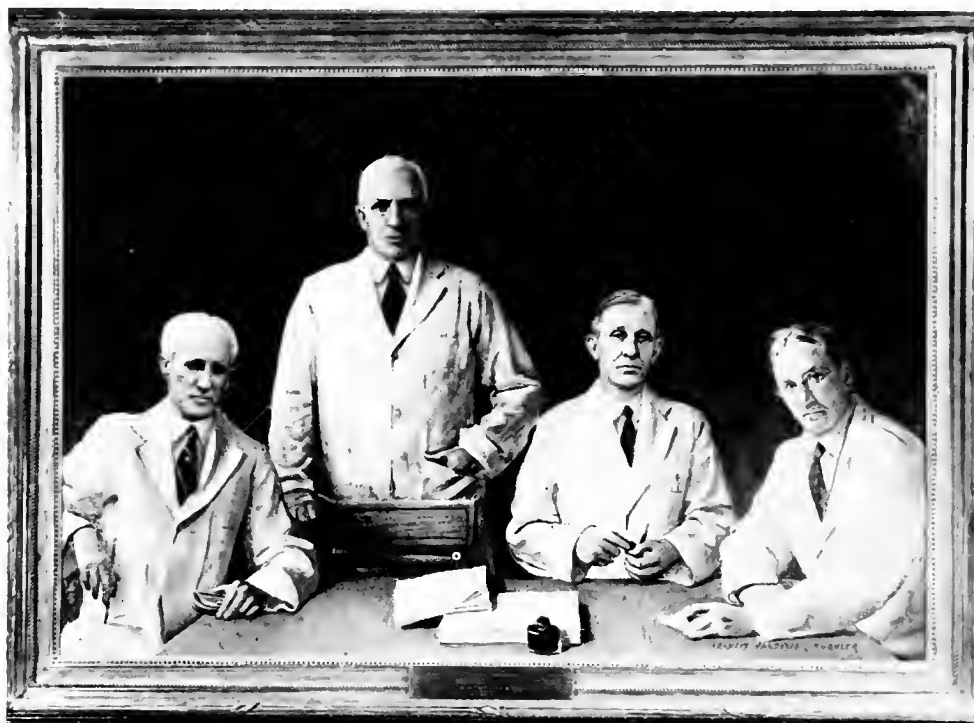
"Do you think, Mr. Bullitt, that it would be necessary for you to drink a whole barrel of whiskey to make a decision?"

I had conversations with Dr. Bullitt about many things, including financial matters. Two stand out in my memory. Both illustrated his belief that rational acts speak for themselves and require no explanation or apology. Dr. Bullitt believed strongly in husbanding his resources against adversity, having lived through at least three severe financial depressions. He pointed out that a well-known weakness of others was spending large amounts of money on unessential things such as expensive clothing. He said that he spent as little on clothing as would allow him to continue to be regarded as dignified. He explained that a man really needed only two suits of clothes if both were approximately alike and of moderately dark hue. One could be worn while the other was at the cleaners. He preferred a salt-and-pepper grey pattern because it did not show stains as readily as a solid pattern. A suit could be worn for many years if it was kept neat and clean, and no one would be aware whether it was old or new. An old one could be replaced by a new one, and no one would be the wiser. I don't know whether Dr. Bullitt actually practiced this policy because I never knew when he was serious and when he was pulling my leg. I wish that I knew, however, because the clothing scheme had obviously been very carefully thought out and had much to recommend it.

On another occasion he told me a story about a stock market deal. Again, I don't know whether the story is true or apochryphal, because I heard it in almost the same words in a Broadway play several years later. Dr. Bullitt stated that at the depth of the Great Depression in 1932 he decided that the country was either going to the dogs or would completely recover. Stock prices were at rock bottom, General Motors, General Electric, Standard Oil, etc. selling for less than \$5 a share. If the country were to disintegrate, he would probably not have to repay his debts. If the country were to recover, he could make a lot of money by investing in stocks. So he went to Durham, borrowed all the money that Mr. John Sprunt Hill would lend, and bought blue chip stocks. He told me this story shortly after I joined the faculty in 1946, by which time such stocks should have divided several times and probably were quoted at \$25-50 a share. Although he never stated that the financial problems of his retirement had been solved by this astute piece of business, such a move would have been completely consistent with his rational approach to life and his decisiveness when action was needed. If the story is correct, it was a very wise move on Dr. Bullitt's part because at his retirement in 1947 the University had not yet developed a pension plan for its faculty members.

When I took Dr. Bullitt's pathology course, it was tough but it was taught in a very simple and straightforward manner. We read the textbook of William Boyd, following his outline chapter by chapter. Our readings were supplemented by Dr. Bullitt's daily lectures, demonstrations of the day's slides on the projector by Dr. Russell Holman, autopsies performed at Watts Hospital at any time of day or night by Dr. Fred Patterson, and Dr. Bullitt's dreaded unknown slides.

Dr. Bullitt was an incredible lecturer. He would appear on the dot of the hour dressed in his grey suit, reach into his left inside jacket pocket and pull out a small set of 3x5 cards. He would turn to a spot marked by a paper clip, place



Portrait of four great leaders of the UNC School of Medicine in the first half of the 20th century. From the left: Charles Staples Mangum, Isaac Hall Manning, James Bell Bullitt, and William de Berniere MacNider.

it in front of him and start talking. He would talk steadily for exactly 40 minutes, put the paper clip at the point he had reached, replace the cards in his pocket, and answer questions. He went through this exercise without apparent effort for two semesters, touching on the major points and illustrating them with anecdotes, many of which dated back to his years in Mississippi. We thought that most of his stories were probably fabricated, because they fitted so neatly into his subject matter; but in any event they were memorable and anything might have happened in Mississippi.

Thirty or so times a year, Dr. Bullitt exposed us to unknown slides, and we played the game of unknowns by very strict rules. Exactly 30 minutes were devoted to the examination of a slide and the writing of a 50-word description of the tissue and the diagnosis. If one did not finish on time, or if the description contained more than 50 words, and "F" was awarded.* This exercise forced students to develop an unusual writing style, one which might be referred to as "Bullitt-English," a form of pidgin English. A paragraph of the approximately correct length was written and the words were carefully counted. Then the paragraph was reduced to exactly 50 words by deletion of a sufficient number of articles and prepositions. Dr. Bullitt

must have suffered from having to read these strange paragraphs, but he retaliated with trick slides, fabricating impossible tissues. We found several of these unknown slide sets after his death. I remember one which consisted of a piece of human liver into which he had inserted the retina of an eye. Since identification of the tissue was the first step in diagnosis, this must have caused much head scratching. I also remember an unknown given to my class with the statement that the tissue had been obtained from a man found dead in bed in Hillsborough. The tissue proved to be from the pancreas. After spending 30 minutes searching unsuccessfully in my textbook for a pancreatic disease which might have caused sudden death, I gambled in desperation on "acute pancreatitis." When Dr. Bullitt returned the graded papers, he explained that the pancreas was in fact normal and that sudden death had resulted from having been hit on the head with a hammer while asleep.

Dr. Bullitt influenced me in other ways. He convinced me that I should smoke a pipe rather than cigarettes, and he taught me wood carving. He pointed out that even cheap pipe tobacco could be made smokeable by humidifying it in a canister which contained an apple. I learned from him about "Old Crop" which was sold at Shields' grocery store on Franklin Street and was dispensed in a cloth bag at \$1 a pound. I shudder to think how my colleagues and family must have suffered during the 15 years I smoked "Old Crop." But woodcarving was innocuous and great fun; it

* A student later to become a prominent surgeon chronically failed to observe this rule. He flunked Pathology and was required to repeat the entire second year. He never again spoke to Dr. Bullitt after having passed the course on the second try.

even prevented me from going insane with boredom at a later point in my career when it became necessary to spend long hours in committee meetings.

Dr. Bullitt carved and polished his wood objects wherever he was, the polishing being particularly obvious at faculty meetings. He was quite unselfconscious about where he did his polishing, because the carvings had to be polished somewhere, and what else could one do at a faculty meeting? The wood polishing led the students to spoof Dr. Bullitt in one of the Student-Faculty Day skits by presenting a mock meeting of the Pathology department in which the student playing Dr. Bullitt would turn on a floor-polishing machine every time the student playing Dr. Brinkhous tried to speak. But Dr. Bullitt was really very thoughtful; he used only fine grain sandpaper at faculty meetings.

He was unfailingly courteous, kind, and thoughtful, and loved children. My children adored him and remember him with great affection. Whenever he saw them at departmental parties or in the halls of MacNider, he always stopped to speak, following which he would toss them high in the air. They remember him as tossing them without removing his pipe from his mouth. They thought that, like Popeye, it was part of his face.

Student Aid was a very small operation at Chapel Hill before World War II and many medical students were on very tight budgets. Dr. Bullitt was known to be always good for a loan when every other possibility had been exhausted. No one knows how many loans he made, but he told Miss Dunlap, the Dean's secretary, that every loan he had ever made had been fully repaid, except one.

Dr. Bullitt was a life-long patriot. He had been a medical officer in World War I and I am certain tried to enlist when World War II began. Since he was in his late 60s and could not be accepted for military duty, he volunteered for the Red Cross, becoming the teacher of first aid for patriotic local ladies. Mrs. Berryhill remembers with amazement watching Dr. Bullitt teach resuscitation to the dignified ladies of the community under circumstances which would have been very amusing had first aid not been such a deadly serious matter to them.

Gasoline was tightly rationed during World War II and Dr. Bullitt had a serious problem. He liked to go home for lunch, but four trips a day from Gimghoul Road to MacNider were too time-consuming on foot and a car required too much gasoline. So naturally he bought a bicycle. Dr. Bullitt on his bicycle — fully dressed, pipe in mouth, hat on head, clips on his ankles, and accompanied by a small beige dog — was an unforgettable sight in Chapel Hill during the war. Unfortunately no one seems to have taken a picture of him in full flight although there is a snapshot of him booted and spurred preparing to ride. At the war's end the increase in auto traffic caused Mrs. Bullitt to become very worried about his safety. She wanted him to give up the bike, but Dr. Bullitt had by now become very attached to bike riding, and it almost required an act of the Legislature to get him to stop.

I think Dr. Bullitt regarded George Penick and me as wild-eyed radicals when we returned to the University from World War II full of one-worldism and sympathy for the downtrodden. George was especially suspect because his



James Bell Bullitt.

father was the bishop of Dr. Bullitt's diocese and the Bishop was thought to hold very advanced views about social issues. We had many arguments about social welfare, racial integration, the atomic bomb, and other important topics of the day. Neither side budged an inch, because all of us were very stubborn, but we always ended our arguments on a friendly note, prepared to stonewall again the next day.

Dr. Bullitt was the most thoughtful of men and in his later years was waited upon by an attentive group of ladies in the medical school whom Mrs. Bullitt referred to as his "harem." Dr. Margaret Swanton, Miss Sara Virginia Dunlap (the Dean's secretary) and Miss Mittie Pickard, his long-time technician, were the frequent recipients of flowers from his garden, or small gifts, and he never forgot their birthdays. They in turn were equally solicitous of him. Miss Pickard, unfortunately, has died but if she were alive and here today she would be sharing in this appreciation. I would expect, however, that she would take me off to one side and chew me out for not having said things exactly the way she remembered them.

Dr. Bullitt appeared in the Department daily until he entered a nursing home in 1962. This was the same year that we occupied the northern extension of MacNider Hall, now known as the Research Wing, and about a decade before we moved into the building we recently dedicated to Dr. Bullitt and Dr. Brinkhous. I have wondered what Dr. Bullitt would have thought of our Preclinical Educational Building. It is tall and one's colleagues are scattered among nine small floors. We have learned that departmental col-

legality is greatly impaired when departmental housing is arranged this way. I know that Dr. Bullitt would have disliked this very much, because he loved to wander around the halls in MacNider inquiring about our welfare and striking up conversations. But Dr. Bullitt always took the rational approach. Looking at all sides of the question, he probably would have opined that a nine-story building connected by eight flights of stairs is not the best arrangement, but it has at least one redeeming feature. One can

remain physically fit by running up and down the stairs!

Dr. Bullitt was a member of the medical faculty, active and emeritus, for more than 50 years. This places him in a very small and select group. The group includes Dr. MacNider, his contemporary. It is very fitting, therefore, to those of us who knew them both that the building bearing Dr. Bullitt's name be adjacent to the one that bears the name of Dr. MacNider.

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Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. Associated widened QRS complex or arrhythmia requires prompt additional therapy. Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and tramterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids) and during concurrent use with amphotericin B or corticosteroids or corticotropin (ACTH). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias: liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving tramterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Tramterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Anti-hypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Tramterene has been found in renal stones in association with the other usual calculus components. Therefore, Dyazide should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on Dyazide when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with Dyazide. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. Dyazide interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with Dyazide, but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and Dyazide should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Dyazide should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth, anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions, nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances, postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics), Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, salivary glanditis, and vertigo have occurred with thiazides alone. Tramterene has been found in renal stones in association with the other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on Dyazide, although a causal relationship has not been established.

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Problems and Prospects for the "Living Will" in North Carolina

John C. Moskop, Ph.D.

JUDGING from the frequency of its revision, North Carolina's Natural Death Act¹ remains a controversial piece of legislation. Since its enactment in 1977, each subsequent session of the General Assembly (in 1979, 1981, and 1983) has seen fit to revise portions of it. Critical reviews of the Act and its amendments have appeared in the state's medical and legal literature.²⁻⁵ Each of the three revisions has improved the Act in important ways. The 1979 revisions recognized the crucial distinction between *allowing* a patient to die and determining that a patient is *dead* on the basis of irreversible cessation of total brain function. The 1981 revisions broadened the Act to provide a legally sanctioned mechanism for *withholding* (in addition to discontinuing) extraordinary treatment from *mentally incapacitated* (in addition to comatose) patients.⁴ The 1983 revisions further refined this mechanism, reducing the number of physicians required to confirm the patient's condition and providing that extraordinary means may be withdrawn or withheld *with the concurrence* of, rather than *at the request* of, the appropriate relative or guardian.⁵

The second and longest section of the Act is its "living will" clause. This clause specifies a mechanism for executing a "Declaration of a Desire for a Natural Death" and shields physicians from criminal or civil liability for honoring such a declaration. Judging from conversations with and observation of physicians who care for the terminally ill, however, the number of persons who have prepared and signed a "Declaration of a Desire for a Natural Death" remains quite small. Because the law has not been widely publicized or promoted, failure to use the "living will" clause may simply be due to lack of knowledge about it. If this is the case, as more and more people learn about the law, more will take advantage of it. Some of those who are already familiar with it, however, are still reluctant to sign a "living will," even though they have no desire that their own lives be prolonged in the sad and hopeless condition that medical technology sometimes permits. In this article, I will suggest some reasons for their reluctance and recommend a different approach in which a person designates someone in advance to make treatment decisions for him when he is no longer able to do so. This approach has recently been reviewed and endorsed in a report of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research.⁶

The North Carolina Natural Death Act

To begin, let us consider what a person authorizes when he prepares and signs a living will document according to the North Carolina Natural Death Act. The Act recognizes the following form as specifically determined to meet its requirements:

Declaration Of A Desire For A Natural Death

I, _____, being of sound mind, desire that my life not be prolonged by extraordinary means if my condition is determined to be terminal and incurable. I am aware and understand that this writing authorizes a physician to withhold or discontinue extraordinary means.

This the ____ day of _____,

Signature _____⁷

With this document in force, if the person's attending physician determines that his or her condition is terminal and incurable (and that determination is confirmed by another physician), the attending physician may, without fear of criminal or civil liability, direct that extraordinary means be withheld or discontinued. Extraordinary means are defined as "any medical procedure or intervention which in the judgment of the attending physician would serve only to postpone artificially the moment of death by sustaining, restoring or supplanting a vital function."⁸

In short, executing this declaration authorizes one's attending physician to withhold or discontinue treatment in a certain situation, namely, when one's condition is terminal and incurable and the treatment would only artificially postpone death. The document gives substantial discretion to the attending physician, since he or she must judge not only when the patient's condition is terminal and incurable (subject to confirmation by another physician) but also which treatments would only prolong life artificially. Because the key words "terminal," "incurable," and "artificial" remain undefined in the statute, it falls largely to the attending physician to interpret the situation and make a treatment decision according to his own understanding of these broad and rather vague concepts. Unlike several other states, North Carolina specifies no penalty for a physician who fails to carry out a written declaration. This may be viewed as a weakness by some, but in view of the very general language of the declaration and the substantial interpretation required by the physician, it would, I think, be difficult to show conclusively that a decision to continue treatment in a particular situation violated the declaration.

Is this a good mechanism for insuring that one's life will not be unduly prolonged (or shortened)? If I knew who

From The Humanities Program, East Carolina University School of Medicine, Greenville 27834.

would be the attending physician making decisions about prolonging my life *and if I knew and trusted this physician's judgment about when life is not worth prolonging and when hope for a cure is not appropriate, then I would be inclined to say yes.* In that case, I would be willing to let my physician decide when no further efforts should be made to prolong my life "artificially." There is, however, no way to guarantee that a particular physician will be there to care for me in the event of a terminal illness or injury. I may, for example, be injured while traveling far from home, or my personal physician may be away when my condition deteriorates. Moreover, some physicians I might otherwise choose to care for a medical or surgical problem are not people I would want to decide about what efforts should be made to prolong my life.

If, then, I execute a declaration according to the Natural Death Act, I authorize the physician attending me in a condition he or she judges to be terminal, whoever that physician may be, to withhold or withdraw "extraordinary" treatment. In order to act on my declaration the attending physician must, of course, know that it exists. Anyone, including myself, my family, or another member of the health care team may give him or her this information. Before acting on my declaration, the physician may choose to consult with my family, but the Act does not require this, and it protects the physician who acts in accordance with my declaration even if this is done against my family's wishes. If, in contrast, I have not signed a declaration, treatment may be withheld only with the concurrence of my spouse, guardian, or a majority of relatives of the first degree, in that order, if any of these are available.⁹ It appears, therefore, that I ought to prepare a living will if I prefer that my attending physician, not my spouse, guardian or relatives, make the decision about withholding or withdrawing life-prolonging treatment, based on a general statement of my desires. I should not prepare a living will if I want to insure that my spouse, guardian or relatives play a significant role in making this decision.

In sum, the North Carolina Natural Death Act offers two procedures for decision-making regarding life prolonging treatment for the terminally ill. On the one hand, I may make a declaration stating my wishes in more or less general terms. This authorizes my attending physician to interpret my desires and honor my wish not to be treated in the general circumstances described. On the other hand, I may make no declaration, thereby leaving decisions about life prolongation to my physician and spouse, guardian or family, should I become incompetent.

Proxy Directives

The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research has recently called attention to a third alternative for making decisions about the prolongation of life. According to this alternative, which the Commission calls a "proxy directive," a person designates someone else to make decisions regarding his or her treatment should the person become unable to make them. Two recently adopted natural death statutes (in Delaware¹⁰ and Virginia¹¹) explicitly

recognize this alternative by providing for the appointment of a proxy or agent and recognizing the proxy's authority to make treatment decisions for the person who appointed him or her. In addition to these statutes, the Commission argues that durable power of attorney statutes existing in 42 states (including North Carolina¹²) may be used to make proxy directives.⁶ Under these statutes, one person (the principal) may confer upon another (the agent or attorney-in-fact) the legal authority to perform certain acts on the principal's behalf, even after the principal is incapacitated or incompetent. Although these statutes were not enacted to facilitate health care decision-making, there is nothing to prevent the execution of a power of attorney for this specific purpose.

Appointment of an agent to act in one's behalf has several advantages over the more traditional versions of the living will. First, it allows the patient's agent to make specific decisions in response to specific developments in the patient's condition. The physician, therefore, is freed from the difficult task of trying to determine, based on only a very general statement of desires in a "living will," what the patient's wishes in a specific situation would be. (The physician, however, will remain responsible for insuring that the patient fulfills the provisions of the natural death statute, e.g., that he or she is in a terminal condition and has made a valid declaration.) Several commentators have viewed this imprecision and ambiguity as a major defect of the living will.^{13, 14}

Second, a proxy directive allows a person to appoint someone he trusts implicitly (perhaps a spouse, a son or daughter, or close friend) to make these decisions for him, rather than rely on a physician he may know less well, or perhaps not at all. The person may also feel more confident in his or her agent's ability to choose the right course of action based on the agent's intimate knowledge of the person and a loving concern for his or her well-being.

The alternative of proxy directives is not without its own disadvantages. There may be practical problems, e.g., the procedure for executing a power of attorney in North Carolina is more cumbersome than that for executing a living will. This, however, is not the case in Delaware and Virginia, the states that have incorporated proxy directives into their natural death statutes. A second and potentially more serious problem is the possibility of abuse of the proxy's authority. Someone might, for self-interest or malicious reasons, pressure a person into appointing him or her proxy for making health care decisions. Alternatively, a person who had, in good faith, agreed to be a proxy might later be faced with a conflict between his own interests and those of the person who designated him proxy. In such instances, a proxy might make decisions contrary to the patient's best interests. Safeguards can be instituted to guard against this possibility, however. For example, the North Carolina Natural Death Act requires that two witnesses attest to the mental competence of the person signing the declaration and that a clerk of court or notary public further attest that the person executed the document willingly and voluntarily.⁷ The Delaware and Virginia Natural Death Acts also circumscribe rather narrowly the kind of situation in which agents may be authorized to make treatment decisions for others. Furthermore, as in cases of child abuse, the physician is responsible to seek to override the

proxy's decision if that decision is clearly harmful to the patient.*

Conclusions

The generality of North Carolina's "Declaration of a Desire for a Natural Death" and the unavoidable uncertainty regarding who will interpret and apply it limit its usefulness as a means for honoring patients' preferences about life-prolonging treatment. A promising alternative included in several recent natural death statutes is the proxy directive, or designation of a person to make decisions regarding life prolonging treatment should one become incompetent. This alternative would give the patient a greater assurance regarding who would make these decisions for him or her. It would also allow treatment decisions to be made in light of the specific circumstances of the patient, thus avoiding the difficulty of trying to apply a general statement of desires to a complex situation. These are good reasons for considering yet another revision of the

North Carolina Natural Death Act to recognize proxy directives for decisions about life-prolonging medical care.

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* For this point I am grateful to Dr. Joanne Lynn.

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An Insight Into Utilization Review: Beyond Responsibility and Toward Accountability* (a mini history of the development and evolution of peer review)

Harold R. Silberman, M.D.

“THE Hospital exists in our society ‘under a contract’ that requires it to exercise reasonable diligence regarding the quality of medical care of all the patients all the time.”

1919: Establishment by the American College of Surgeons (ACS) of its Hospital Standardization Program.

1940: ACS moved to actual review of patient care by tissue committees, followed quickly by antibiotic and later transfusion committees.

1965: *Darling* case adjudicated in Illinois (*Darling v. Charleston Community Hospital*): not the passage of a new law, but a Court’s interpretation of society’s position and the expanding responsibilities of hospitals as institutions, thus changing their relationships with staff physicians.

1965: Utilization review said to be required under Medicare with the focus on peer review.

1972 (early): American Hospital Association announced QAP, its Quality Assurance Program.

1972: Joint Commission on Accreditation of Hospitals initiated its TAP institutes (trustees-administrators-physicians) and informed hospitals as well as their medical staffs that they would be expected to control the quality of care if they were to be accredited.

1972 (late): Congress enacted Public Law 92-603. That act made the hospital itself responsible for the quality of its care and called into being Professional Standards Review Organizations (PSROs). Their mission: to determine for all patients treated under Medicare, Medicaid, and Title V of the Social Security Amendments whether the care was reasonable, medically necessary, of recognized (professional) quality, and provided in the proper facility.

“... duty and function of each Professional Standards Review Organization . . . to assume . . . review of the professional activities . . . in the provision of health care services and items for which payments may be made (in whole or in part) . . . for the purpose of determining whether —

- (A) such services and items are or were medically necessary;
- (B) the quality of such services meets professionally recognized standards of health care; and
- (C) in case such services and items are proposed to be provided in a hospital or other health care facility on an in patient basis, such services and items could, consistent with the provision of appropriate medical care, be effectively provided on an out patient basis or more economically in an in patient health care facility of a different type.” (PL 92-603 SEC. 1155) [A][1]

1974: PSROs in place and required under the Act to accept the hospital’s efforts (through its several review committees) at monitoring services/care “to the extent that they did the job in acceptable manner.” (*italics mine*)

1974-1982: Methodological problems brought changes and new vocabulary: concurrent admission (or preadmission) certification; concurrent continued-stay review of extended-stay cases; retrospective review; focused-out review (necessitated by financial constraints placed upon PSROs by federal funding cuts), etc., etc.

1982 (September): Peer Review Improvement Act of 1982 (sections 141 through 150 of Public Law 97-248, the Tax Equity and Fiscal Responsibility Act [TEFRA], enacted September 3, 1982) created a new Federal authority to fund utilization and quality control peer review organizations to be known as PROs. This new act replaces a 1972 amendment to the Social Security Act which created Professional Standards Review Organizations (PSROs). Part of this so-called TEFRA initiated prospective payments at a fixed rate until the next step.

1983 (April): PL 98-21 provides for a prospective payment concept that was implemented by the methodology of DRGs. Most hospitals began this approach by October 1, 1983, depending on the timing of their fiscal years.

When Congress passed prospective payment laws, it expressed its will that the Federal Government take a bold step to curtail rising hospital costs and to protect the solvency of Medicare for future generations.

1983 (October): Prospective payment, at “flat rate” per patient, replaced cost-based reimbursement system at Duke.

* \$35 billion in public funds paid out each year under Medicare Part A to 7000 hospitals because of 350,000 physicians providing in-patient care to this country’s elderly and disabled beneficiaries.

From the Department of Medicine, Duke University Medical Center, Durham 27710.

In this climate, HCFA (Health Care Financing Administration) instructs PSROs to drop both review of whether ancillary services are appropriate and the traditional analysis of lengths of stay, advising instead assessment as to whether an admission is needed and where stay is excessively long or costly, PSROs are to review for *unnecessary care*.

1984 (July): Duke and some other hospitals with similar fiscal year dates begin prospective payment (partially -25% per case) for first year via a system of 467 diagnosis-related groups (DRGs).

1985: By this date, DRG legislation requires the Secretary of Health and Human Services to report on the "advisability and feasibility of applying DRGs to physician charges for hospital services and to recommend legislation to apply the DRG concept to physicians."

Again the key issue for review groups would be whether or not a hospital stay is really indicated.

1987: DRG rates should be fully phased in over the previous 3 years.

Educators know and are frustrated by the fact that auditing is not necessarily carried out for the purpose of adding to medical knowledge, but simply to see if current medical knowledge is being applied; and if not, why not and what can/must be done about it.

Hospitals must recognize that PSRO/PRO legislation does not alter the hospital's legal responsibility for review and maintenance of quality as established under statutory law and case law nor does it abrogate the requirements to comply with JCAH/AHA criteria for accreditation.

After considering the evolution to this state of affairs a physician might be more receptive to one writer for the Sounding Board column in the *New England Journal of Medicine* (Platt R: NEJM 1983; 309:726-730) "are we ready for these kinds of changes? Should we be? Perhaps we ought to be less concerned about cost containment and more prepared to spend 12 or 13% of the gross national product on health care by 1990. What we should not do is pretend that *painless* cost containment is an achievable goal."

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An Encouraging Word on the Socioeconomic Front

William J. DeMaria, M.D.

LINCOLN County physicians were notified in December 1982 of a significant change in medical insurance benefits by a major employer in their county.

The company, Mohican Mills of FAB Industries, alarmed with their increasing costs of medical services, reviewed the utilization and cost data provided by their insurance carrier, Blue Cross and Blue Shield of North Carolina. It was agreed that an immediate and radical change in benefits was necessary if control of escalating costs was to be attained.

The new benefits package includes a \$200 deductible for each hospitalization with a 60-day renewal period. There is a 100% usual, customary and reasonable payment not subject to deductibles for hospital and doctors' charges for outpatient treatment of accidental injury within 72 hours, outpatient treatment of medical emergencies within 72 hours, outpatient surgery, and outpatient diagnostic services. Reimbursement for inpatient services is at 80%, clearly providing an incentive for treatment on an outpatient basis whenever possible.

A preferred provider arrangement was made due to the presence of two hospitals in the community, a for-profit institution with average charges per day 79% greater than at a neighboring not-for-profit hospital. To encourage employees' use of the lower cost hospital, the inpatient deductible is only \$100 for this preferred provider.

In addition, a pre-admission certification program was selected as an acceptable way of putting brakes on both the user and provider in an area where studies had shown that significant hospital overutilization existed. The pre-admission certification requires the physician's office to

request certification for all elective admissions other than for emergency and obstetrical problems. Certification is accomplished by the physician's office calling a designated collect number at the Blue Cross and Blue Shield of North Carolina Service Center where registered nurses with physician consultant backup make the decision regarding reimbursement for elective admissions. The primary purpose is to encourage ambulatory surgery, decrease weekend admissions, conduct pre-admission studies in ambulatory settings and decrease admissions for routine studies which can be conducted in an ambulatory setting.

Results of the first six months are encouraging. The rate of hospitalization for these employees as measured in days per/1000 persons has decreased by a significant 20%. In addition, the preferred provider arrangement has resulted in approximately one-third fewer admissions to the high cost hospital in contrast to the same time period in 1982.

We present this note to encourage physicians in North Carolina to join private industry in developing cooperative programs which aim at slowing the disproportionate rise in health care cost. In addition, we wish to note formally that this successful introduction of pre-admission certification in North Carolina could not have been achieved without the cooperation of physicians in Lincoln County. We realize that physicians are reluctant to add yet another administrative step in conducting medical care for their patients. Increasing numbers of physicians do agree, however, with the need to demonstrate their willing cooperation in cost containment programs. These cooperative ventures are essential if integrity of private practice, quality of care, and coveted patient-physician relationships are to be maintained.

Among the dizzying and confusing events ongoing in the medical care arena, it is most reassuring to provide the *Journal's* readers with an encouraging word.

From Blue Cross/Blue Shield of North Carolina, P.O. Box 2291, Durham 27702.

Medical Exorcism — Acute Dilantin Intoxication

Ronald B. Mack, M.D.

SEVERAL centuries before Christ, Hippocrates stated the brain was the organ involved in epilepsy; his fellow Greeks, however, believed that this disease was caused by supernatural forces. In the first monograph concerning epilepsy that we know about (entitled *The Sacred Disease*), Hippocrates publicly assailed the citizens of his country for believing that the disease was "sacred." He attacked the wizards, magicians, charlatans, et al. who, he said, hid their ignorance and fraudulent practices behind the cloak of the divinity of epilepsy.¹ Hippocrates believed that a generalized convulsion is always to be regarded as a serious omen until a thorough examination of the afflicted person and the passage of time have proved it to be but an incidental symptom of some transient or curable disease.

The theory that the body could be taken over by supernatural, malevolent forces was still very popular in the Middle Ages where it was widely believed that people's bodies could be inhabited by demons. Epilepsy (called the "falling sickness" in that period of history) was thought therefore to be due to demonic possession. It probably wasn't until the 19th century that reason entered the minds of clinicians when Jackson identified, in 1870, the cerebral cortex as the site of disturbance in epilepsy. Even in the enlightened 1980s there are some who view the epileptic as "unclean." Modern therapeutic modalities attempt, in a sense, to get rid of the "demons" that cause the "falling sickness."

Of the various chemicals used to exorcise an epileptic from his/her misery, *phenytoin* (Dilantin, formerly known as diphenylhydantoin — DPH) is one of the best known and prescribed anticonvulsants. The value of this drug in the therapy of epilepsy was first reported in 1938. Because of this drug's remarkable power and efficiency you might think that it would produce devastating effects if taken in overdose. In fact, fewer than 10 deaths have been reported in this country from acute or chronic phenytoin overdose from any route of administration. Accidental childhood overdose from this drug is surprisingly uncommon, considering its availability, and when it does occur is usually a relatively mild event.

In therapeutic doses, drug absorption is slow due to its limited solubility in the GI tract, and peak serum levels after a single oral dose occur in 6-12 hours. It takes 6 to 9 days of daily medication to achieve a steady-state condition. After absorption the drug is hydrolyzed by the liver, conjugated with glucuronide and excreted in the urine and bile. Less than 2% of this drug is excreted in the urine unchanged. The $T_{1/2}$ (half life) of a therapeutic dose in

healthy adults is $22 \pm$ hours but children metabolize the drug more rapidly. For those of you who are "squeamish" the next two paragraphs may be skipped. I am not prejudiced against "squeams" and I hope I will not get letters from the Squeamo-American Society.

The *toxicokinetics* (there's that word again) of phenytoin is both fascinating and useful in terms of the clinical course and management of the overdosed patient. The $T_{1/2}$ is dose dependent, i.e., the time required for the plasma level of this drug to halve increases as the concentration of the drug increases. In therapeutic doses, elimination of phenytoin follows what is referred to as *first-order kinetics*, i.e., the transfer of a constant fraction of a drug per unit of time. Thus the rate of transfer in first order kinetics is directly proportional to the amount of drug remaining to be processed. In such a process a drug with a $T_{1/2}$ of 8 hours and an initial concentration of 40 $\mu\text{g/ml}$ will have a concentration of 20 $\mu\text{g/ml}$ 8 hours later and only 10 $\mu\text{g/ml}$ 8 hours after that and so on.

In the patient acutely overdosed with phenytoin a different kinetic elimination process occurs, known as *zero-order kinetics*. In this process, elimination occurs at a *fixed* rate regardless of the amount of drug remaining instead of at a rate proportional to the concentration of drug present as in first-order kinetics. Under zero-order kinetics, with higher doses, the plasma level of phenytoin increases disproportionately. Why is this true in acute phenytoin overdose, you ask? Probably because the enzyme systems needed for elimination of this drug are saturated with larger doses and elimination is impaired. As a general rule, with drugs requiring hepatic enzymes systems for detoxification these enzymes have the potential to be saturated. The concept of enzyme saturation explains why serum levels decrease quite slowly following a large overdose, but then these same levels decrease more rapidly as the serum concentration falls. Simply stated, when a patient incurs an overdose with phenytoin, the clinical features of toxicity may persist for days until the metabolic rate of elimination increases and phenytoin levels decrease below the toxic range.

The typical clinical features of a patient acutely overdosed on phenytoin consist of the well known triad of *nystagmus*, *ataxia*, and *drowsiness*. Most of the adverse clinical findings are confined to the central nervous system. The earliest detectable sign of acute overdose is *nystagmus* on lateral gaze. A plasma phenytoin level taken at this time will probably be $> 20 \mu\text{g/ml}$ (a therapeutic phenytoin level is 10-20 $\mu\text{g/ml}$). With increasing accumulation of the drug, progressive spontaneous horizontal nystagmus occurs. When the level exceeds 30 $\mu\text{g/ml}$ ataxia ensues. The most striking and fairly consistent toxic effect of phenytoin

From the Department of Pediatrics, Bowman Gray School of Medicine, Winston-Salem 27103.

seems to be on cerebellar function. As the level rises > 30 $\mu\text{g/ml}$ nystagmus can become vertical, speech becomes slurred and drowsiness is often present. The gross ataxia and incoordination of the trunk and limbs produce a lurching gait in the patient, with a rather characteristic coarse tremor of the extremities on voluntary movement. This incoordination frequently progresses to the degree that patients cannot walk and some cannot even stand. With even more increased dosage consciousness may be depressed to the extent that the patient is not only drowsy, but confused and disoriented often with hyperactive or manic behavior. A totally unresponsive state is really quite uncommon and respiratory depression is also unusual. If you suspect phenytoin overdose in your patient and the patient is in coma, look for another cause. The deep tendon reflexes are normal or increased and the pupils may be dilated.

It is easy to see that if you are confronted by a patient with nystagmus, ataxia, hyperactivity, and disturbances in consciousness and you don't have a history of drug overdose you might consider other diagnoses. Certainly the possibility of a posterior fossa tumor must enter your consciousness as well as acute viral cerebellitis, Guillain-Barré Syndrome, botulism, hysteria, and a host of others as they say. Choreoathetosis has been described with acute phenytoin overdose and quite closely resembles Sydenham's Chorea. It is fair to state, however, that the most common cause of acute ataxia in all age groups is overdose of intoxicating drugs or toxic compounds.

Phenytoin is an effective antiarrhythmic drug useful in controlling abnormal rhythms in overdoses due to drugs such as digitalis and tricyclic antidepressants. Phenytoin apparently stabilizes membranes and thus prevents the spread of seizure discharges in the CNS, but in the cardiovascular system this characteristic of membrane stabilization can decrease the automaticity of the SA node and increase AV block. Cardiovascular toxicity with this drug is generally limited to patients receiving rapid IV infusions or in massive oral overdose. The cardiovascular effects of phenytoin include a decreased rate, an increase in AV block, ventricular fibrillation, direct myocardial depression, decreased cardiac output leading to congestive heart failure, idioventricular rhythm, hypotension, asystole and death.

The diagnosis depends of course on a good thorough history and physical exam plus serum phenytoin levels. Because of protein binding, age, race, and a bunch of other factors, exact correlation between serum phenytoin levels and toxicity probably do not exist; however, levels < 15 $\mu\text{g/ml}$ are rarely associated with toxicity and levels > 95 $\mu\text{g/ml}$ have been associated with fatalities. In this poisoning the EEG shows slowing of the alpha waves but of course this is not specific for this poisoning.

The treatment of acute phenytoin overdose is fairly straightforward: (1) withdraw the medication if the patient is taking the drug on a chronic basis, (2) obtain serial serum phenytoin levels, (3) carefully monitor the patient. In an emergency room encounter with a patient involved with an acute phenytoin overdose, gastric emptying is indicated

followed by administration of activated charcoal and a saline cathartic such as magnesium sulfate. In very severe overdoses involving this drug the use of hemodialysis to increase the elimination of phenytoin is probably an exercise in futility; the protein binding of phenytoin is extremely high and dialysis probably is not going to benefit the patient very much (it won't do much for the poison-treater either). Charcoal hemoperfusion may be of value in some problem overdose cases although good data are not available, in my opinion, to champion its use. Fortunately the prognosis for phenytoin overdose is really quite good without heroic measures. Most of your patients will get better with little more than gastric emptying, charcoal, a cathartic, and observation.

The cardiovascular problems resulting from acute overdose can be treated as follows: (1) Complete heart block can be overcome with intravenous atropine. (2) Effective cardiac rhythm and output have been reported improved following the administration of epinephrine. A temporary pacemaker can be used if the usual measures fail. (3) Hypotension could be remedied by correcting volume deficits and, if this fails, administering (+) inotropic agents such as dopamine.

It would be unfair to the reader to leave this subject without mentioning the peculiar phenomenon of *paradoxical intoxication*. This has been defined as the situation in which seizure frequency increases as the serum level of the phenytoin increases. In the usual case of this unusual state although the phenytoin level can be quite elevated there are few or no toxic features such as nystagmus or ataxia. You could possibly expect to see this condition in patients on chronic phenytoin therapy. The treatment for the seizures should not include giving more phenytoin but rather stopping the offending drug and administering a drug like diazepam. The diagnosis of paradoxical intoxication depends on your thinking of it and obtaining a serum phenytoin level.

Epilepsy is certainly a disease state that has been a mystery since people first became aware of differences in the behavior of their neighbors. Through several millennia the causes of this malady have given rise to many theories and treatments which we look upon today as being bizarre. What will the medical historian of the future think of our "modern" medicine? Will they think of our numerous blood tests for the diagnosis of epilepsy and monitoring for anticonvulsant levels as nothing more than blood-letting to get rid of "evil humors"? Will they view the electroencephalogram as a form of "medical" trephining? Will they think of our anticonvulsant armamentarium as chemical exorcism? I have seen neurology residents, when treating an unresponsive status epilepticus, make a cross from two tongue depressors and place it in front of the convulsing patient in an effort to stop the process. I personally believe that a garlic amulet works better.

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Features for Patients

Income Maintenance in Retirement and the Need to Rethink Family Policy

Angela M. O'Rand, Ph.D.

Background

In 1977 the dependency requirement of the Federal Old-Age, Survivors, and Disability Insurance Benefits program was eliminated. This provision was enacted, in part, as a response to the Supreme Court Decision in *Califano v. Goldfarb*, which found gender-based distinctions regarding survivors benefits to be in direct violation of the Due Process Clause of the Fifth Amendment. Leon Goldfarb, a retired federal employee, had been denied widower's benefits from his deceased wife's social security since he had not been receiving at least one-half support from his wife at the time of her death. This dependency requirement for survivor's benefits did not apply to widows as well.

Califano v. Goldfarb determined this denial to have deprived Hannah Goldfarb, his deceased wife, of her entitlement to protect her family. Hannah Goldfarb had worked in the New York City public school system for nearly 25 years until her death in 1968 and had paid all social security taxes in full during her tenure. The Supreme Court decided that she "was entitled to the dignity of knowing that her social security tax would con-

tribute to their joint welfare . . . and to her husband's welfare should she predecease him" (Kay, 1981: p. 81).

Although this case focused specifically on the issue of dependency benefits under Social Security, it also pointed to the general pattern in our society to ignore the marital bond as a symmetrical economic partnership, in which both partners are entitled to share equally in their joint earnings, savings and investments not only during the life of their marriage but also after it has been dissolved. The failure to recognize marriage as a symmetrical economic partnership, regardless of the divisions of labor followed by the couple, has discriminated against widowers in the past and continues to create special problems of economic dependence for all surviving spouses and former (divorced) spouses who cannot easily qualify for benefits from either Social Security or private pension plans that exclude them. Since women are overwhelmingly represented in these categories, they continue to be victims of a discriminatory family policy embedded in the law, in the practices of governmental regulatory and service agencies and in private firms. But, as *Califano v. Goldfarb* illustrates, such a family policy also discriminates ultimately against men.

Inadequacy of Current Policy

Current policy generally does not recognize women's economic contributions to their families, whether

or not they participate in the paid labor force. Homemakers and unpaid workers in family businesses are notable examples of family partners whose economic roles are ignored. But, as was true for Hannah Goldfarb, women who are or have been paid workers are still treated as non-economic contributors to the family. Such an implicit family policy is inconsistent with women's lives and with the needs of their families.

This article provides a background for and the prospects of changing this inequitable policy, particularly as it applies to the income maintenance problems of older women today and in the future. This overview begins with a profile of an illustrative cohort of women born in 1914 who reached age 65 in 1979. Their experience across the life course and at retirement forms the vanguard experience for formulating and assessing future policy decisions regarding family economic roles and retirement programs. Then, recent proposals supported by the 1983 National Commission on Social Security Reform pertaining to the concept of "earnings sharing" are reviewed as exemplary for rethinking the family policy required for the future.

The 1914 Birth Cohort of Women in the U.S.

Women born during the second decade of this century experienced the depression as young women,

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World War II as young workers, and the fifties as mothers of the leading edge of the baby-boom generation. Their lifetime experience as a cohort was shaped by the major parameters that still define the lives of many women today. Increasing labor force participation, a higher divorce rate and the persistent earnings gap between the sexes have characterized their lives. The figures in table 1 profile their lives in these areas. Women born around 1914 are followed in five-years intervals, starting in 1950 when they approached midlife.

Overall, women in this cohort have led heterogeneous work and family lives. Since 1950, at least half of the women in this cohort have been out of the labor force at any given time. The mid-1960s mark the period of the highest labor force participation of this group, about 49 percent. The median earnings level achieved by these women has never exceeded half of men's median earnings in the same age group. In the 1970s, women in this group came closest to their male counterparts' earnings level, about 49 percent.

Two types of factors account in large part for these labor force and earnings patterns: family role demands and restricted occupational and industrial opportunities. Research on the life histories of women in this cohort shows that they have

tended to interrupt or to delay their work careers in response to child-bearing and childrearing roles. These role schedules at home, at work, or both have slowed their progress, as a group, in earnings achievement and in pension eligibility. However, even when women's role schedules are taken into account, the kinds of occupations and industries in which they are able to find jobs are characteristically low wage and limited in career opportunities. Four out of five clerical workers and nearly two-thirds of service workers are women. In 1970, when the 1914 cohort of women were in their midfifties, over half of those in the labor force at that time were located in either low-level clerical or service jobs.

The notable third pattern in these women's adult lives that can be observed in table 1 is their cohort experience of increased divorce over time. Younger cohorts of women have experienced much higher rates of divorce; but the 1914 cohort of women have also participated in the long-term secular trend of increasing divorce rates. In the 1950s about 4 percent of those ever-married in this group were divorced; by the 1970s, when the most spectacular increases in divorce rates in the United States were witnessed, this cohort's rate had also increased to about 6 percent. These figures, of course, underesti-

mate the rate of those ever-divorced in this cohort, which has been determined to be about 16 percent.

Two to three million women were estimated to fall into the category of "displaced homemakers" by the end of the 1970s. Most of these women were over the age of 50 and had pursued lifestyles to that point which had assumed that their marriages would provide their lifetime needs in retirement, health and social support. Accordingly, they had invested their lives as unpaid workers at home until, for many, widowhood, separation or divorce changed their circumstances.

The Outcomes of Three Problems

These three patterns — labor force participation, earnings history and divorce rate — take on a special importance for retirement income. Lower levels of labor participation and earnings work against individual retirement savings. This occurs because retirement benefits are (1) tied to minimum tenure requirements for vesting and eligibility, (2) calculated on the basis of preretirement earnings levels, and (3) unavailable to large segments of workers (particularly women and blacks) in industries characterized by very poor pension opportunities. The results are that women are half as likely as men to be covered by private or government

Table 1
Labor Force, Earnings and Divorce Histories of Women Aged 65 in 1979 For Period Between 1950 and 1979

Years of Observation of 1914 Birth Cohort (Aged 65 in 1979)	(approximate age)	Percent of Cohort in Labor force ^a	Annual Earnings ^b		Percent of Divorced to those Ever Married ^a
			Median Earnings (\$)	As Percent of Men's Earnings in Same Cohort	
1950	(36)	34.0	1297	41.8	3.9
1955	(41)	40.5	1706	41.0	
1960	(46)	47.4	2205	44.5	4.6
1965	(51)	49.4	2715	45.8	
1970	(56)	47.4	3747	48.8	5.4
1975	(61)	34.5	5020	48.2	
1978	(64)	33.6	5108	46.2	6.4
1979	(65 +)	8.3	—	—	3.9

^a Labor force rates and divorce rates drawn from Tables C.4 and C.7 and B.6, respectively, in George Masnick and Mary Jo Bane's *The Nation's Families: 1960-1990*, Joint Center for Urban Studies of MIT and Harvard University, Cambridge (1980), pp. 174, 183 and 153.

^b Earnings data based on estimated averages for cohorts born between 1911 and 1915 reported in Table 36, *Annual Statistical Supplement*, 1981, *Social Security Bulletin*, 45 (November 1982) p. 90.

pensions at retirement and that Social Security benefits based on their own earnings records are often lower than 50% of their spouses' benefits.

The chief advantages for women of the Social Security system are that the system is nearly universally available (more than 90 percent of the paid labor force is covered by the system) and redistributive features of the system favor low-wage workers in benefit returns (although the regressive wage tax during the working years hits the lower wage worker harder). In the private sector, however, pension plans vary widely in their "benefit promise," that is, in the extent to which workers can successfully qualify for final benefits and in the level of benefits that can be achieved. Workers in the financial, communication, transportation, utilities, insurance, real estate, and selected manufacturing (usually unionized) industries have greater benefit promise, while those located in construction, wholesale and retail trade and service (especially personal service) sectors have much less benefit promise. Women and non-whites are overrepresented in the latter sectors.

Furthermore, if a retired woman is widowed or divorced, she may lose eligibility for her former spouse's retirement benefits from all sources. Few private pension programs provide survivors' benefits; when they do they require the primary retiree to have met eligibility requirements fully, to have stayed married to the survivor, not to have died too soon, and/or to have reduced his/her own benefit as a provision for the survivor(s). This last provision usually is presented as a "joint/survivor option" to the worker; thus automatic post-retirement survivors' benefits are not widely available. Under Social Security a divorced woman can qualify for a 50 percent dependent benefit from her former spouse's account only if the marriage lasted at least 10 years and only when the former spouse himself retires. Under private pension plans, divorced persons have

no protection at all.

The prevalence of poverty among older women expresses one outcome of women's disadvantaged benefit status. By the late 1970s, two out of three persons aged 65 or more who fell below the poverty line were women. About one out of three non-married (widowed, divorced, separated) women over 65 fell below the



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The median earnings level achieved by these women has never exceeded half of men's median earnings.

poverty threshold. And, of all aged persons receiving Supplemental Security Income (SSI), the program established in 1972 to assure a minimum income to the eligible aged or disabled person living in his/her own household, three out of four are women.

Thus, the life course experiences of women reaching old age in 1979 point to limited opportunities for individual retirement saving among

women and to an implicit family policy underlying retirement programs that ignores women's economic contributions to the family. This leaves the older, unmarried (widowed or divorced) woman in triple jeopardy with respect to poverty. Her family role has limited exchange value during marriage and even less after the marriage has ended.

Toward a New Policy: Earnings Sharing for Income Maintenance

Since its introduction in 1976 by House Representatives Martha Keys and Don Fraser, the concept of earnings sharing has gained increasing support as the best solution of problems of retirement coverage of men and women alike. The 1983 report of the National Commission on Social Security Reform reiterated the recommendations of the 1979 Advisory Council on Social Security and the 1980 President's Commission on Pension Policy by noting the following:

... Earnings sharing is a recognition of marriage as an economic partnership with equal respect given to the division of labor chosen by each couple. It accords the right to each individual to a retirement income based on half of the total retirement credits earned by the couple during their marriage. This is similar in concept to the sharing of income in the joint tax return of a married couple. Working women would have a continuous record of Social Security credits when they retire instead of zero credits for years spent in the home. It would respond to, and recognize, the economic value to the couple of full-time work in the home by either spouse. (1983: pp. 16-17).

In addition to protecting the homemaker, earnings sharing also provides the simple formula wherein either spouse benefits from the retirement credits of the couple as a unit. Thus, a wife working under Social Security and a husband not covered by Social Security in his employment



Ernest Crage

Workers in retail trade and service (especially personal service) sectors have much less benefit promise.

(remember Leon Goldfarb) both receive credit from her coverage. The extension of the earnings sharing concept to private and public pension systems would follow the same principle. Should the marriage be dissolved for any reason, the investments by both spouses during the period of their union continue to be recognized officially for earnings credit and survivor benefits purposes.

Table 2 summarizes selected features of the provisions for retirement benefits under the present law and under an earnings sharing proposal. The table's contents are drawn from hearings before the Task Force on Social Security and Women of the Subcommittee on Retirement Income and Employment and the Select Committee on Aging of the House of Representatives on the Treatment of Women Under Social Security, conducted between May 16 and August 13, 1979. The earnings sharing option proposes to redefine the economic division of labor of marriage by treating both partners as economic

contributors to the family unit, by eliminating the concept of "dependency," and by not penalizing single workers or higher earners before or after marriage.

Earnings credit and eligibility for retirement benefits from Social Security are provided to the couple for the period of their marriage during which at least one of them has covered employment. Individual earnings records would be maintained for couples to protect individuals from income loss due to inevitable marital dissolution. Surviving spouses thus can benefit continuously from the standard of living achieved by the couple. The aged homemaker is not treated as a dependent, but as a retired partner of the retired worker; the division of labor adopted by this couple is not penalized. Finally, the divorced person is protected as well.

Prospects for the Future

Trends in labor participation, marriage and divorce observed in different cohorts of women in this century

accentuate the problematic features of the 1914 cohort's experience. Older women in the future will approach their 65th birthdays in larger numbers with higher rates of work and divorce. The same is true, of course, of older men in the future. Public and private policies towards the family can serve to exacerbate or to ameliorate the problems of the future elderly.

While earnings sharing does not resolve all the problems of higher dependency ratios, sex discrimination, variable pension systems across industrial sectors, and poverty among the elderly, it does adopt a definition of marriage as a partnership and thereby anticipates a structural problem in income maintenance among the elderly. Earnings sharing adjusts for the variability in the family and work lives of both men and women without penalizing segments of the elderly population for choosing a particular lifestyle. Finally, it simultaneously protects the individual worker and homemaker from precipitous income loss as a result of a change in marital status. As such, earnings sharing represents a useful redefinition of the family for public policy purposes.

Table 2
Comparison of Major Provisions Under Present Law and Earnings Sharing Option*

Provision	Present Law	Earnings Sharing
Eligibility for retirement benefits	Person must have worked in covered job long enough to be insured for benefits or be a dependent of such a person.	At least one spouse must be insured as under present law.
Earnings credit	Person gets earnings credits based only on his/her own work in covered employment.	Total earnings of married couple divided equally between them for each year of the marriage and credited to their individual earnings records. Surviving spouse credited with 80% of earnings credits of couple (or 100% of higher earner's credits).
Benefits		
A. Retired worker (married, separated or divorced)	Gets weighted benefit based on own earnings credits.	Gets weighted benefit based on half of couple's earnings credits while married and own earnings credits while single, plus any credits acquired as a result of a prior marriage.
B. Aged homemaker (married, separated or divorced)	Dependent spouse's benefit equal to 50% of retired worker's benefit.	No dependent spouse's benefits; gets benefits based on any earnings credits acquired through work or marriage.
C. Aged widow(er)	Dependent's benefit equal to 100% of deceased worker's benefit.	No dependent surviving spouse's benefit; gets benefit based on earnings record as described above (including credits inherited when spouse dies).

* This table is drawn from the U.S. House of Representatives, *Hearings on the Treatment of Women Under Social Security*, Select Committee on Aging, Washington, D.C., Government Printing Office (1980), Table 3, pp. 137-138. The source table described another option and includes provision information on children, mother's and father's benefits, young widows and disabled persons.

Postscript

This essay has not addressed the very important (and related) issue of health maintenance in retirement. As in the case of income maintenance, lifetime patterns of living and structurally mediated opportunities for promoting health and for coping with acute disease episodes and chronic illness influence status in later life. For women, who live longer but not necessarily healthier lives than men on the average, the prospects for suc-

cessfully coping with age-related disease patterns (e.g., osteoporosis, diabetes, and cancer) are related to their economic and marital circumstances. Much more research is needed on the variable and predictable features of these problems.

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Breast Feeding and Cold Medications

Steve Saxe, R.Ph.

The common cold, also known as acute rhinitis, infectious rhinitis, grippe, catarrh or coryza, is caused by one or more invading viruses. The symptoms usually last 7-10 days. Patients frequently complain of feverishness (but seldom fever), generalized discomfort, runny nose, sore throat, headache, cough or congestion. Because a cold is caused by viruses there is no "cure." The cold medications that have been marketed are designed to decrease the severity of these cold symptoms.^{1, 2}

For most people the selection of a cold preparation is relatively easy. For women who are breast feeding, however, the choice is not so simple. Many medications are found in breast milk in sufficient quantities to affect the infant. Since the common cold has no cure, avoiding all cold medications is the best plan when breast feeding. Various nondrug treatments may help relieve some of the cold symptoms. Use of a humidifier and drinking plenty of fluids will help nasal stuffiness and chest congestion. Moist heat packs to the face

may help relieve painful sinuses. Sucking on a hard candy may relieve a sore throat. Also, eating well and getting plenty of rest will help the body fight the cold and produce enough milk.^{1, 2}

If a cold medication must be used, the ingredients should be carefully checked. Long-acting preparations should be avoided and the smallest effective dose should be taken. The medication should be taken right after nursing, and a close watch on the infant and the supply of milk should be made for any signs of adverse effects. The infant may show signs of irritability, sleep disturbances, excessive drowsiness, tremors or subtle changes in behavior, while the mother's supply of milk may decrease. Most important is to remember that medications will not cure the cold, only make it more tolerable.

The common ingredients found in cold preparations include antihistamines, decongestants, expectorants, cough suppressants, pain and fever medications. Unfortunately, the interest in studying the elimination of these drugs in breast milk is fairly recent and good information is lacking. This article will present the avail-

able data to help the nursing woman make an informed decision.

Histamine is released as a result of the reaction between the body's defense system and a foreign substance. This type of reaction is usually seen with pollen-induced allergic rhinitis. Allergic rhinitis is often treated with antihistamines which block the histamine-induced runny nose. The runny nose of a cold is not felt to be caused by histamine. However, one of the effects of antihistamines is the ability to dry up mucous secretions which may relieve the runny nose.¹

Chlorpheniramine, brompheniramine and diphenhydramine are the antihistamines usually used for allergies or cold symptoms. In general, antihistamines are not found in large enough quantities in breast milk to affect the infant. Because of their ability to decrease various secretions, antihistamines could decrease or stop the supply of breast milk. There is no documentation to support this inhibition, but it is a risk that must be considered.^{3, 4}

Decongestants are the most common ingredients in cold medications. They work by constricting blood vessels which, in turn, cause a shrinkage

From the Department of Pharmacy Services, Moses Cone Memorial Hospital, Greensboro 27401-1020

COMMON COLD MEDICATIONS

Product	Dosage	Decongestant	Antihistamine	Pain and Fever	Other
1. Alka-Seltzer Plus	Effervescent tablet	Phenylpropanolamine 24.08 mg	Chlorpheniramine 2.0 mg	Aspirin 324 mg	
2. Chlortrimeton	Tablet		Chlorpheniramine 4 mg		
3. Cantac	Time capsule	Phenylpropanolamine 50 mg	Chlorpheniramine 4 mg		
4. Caricidin	Tablet		Chlorpheniramine 2 mg	Aspirin 325 mg	
5. Ca-Tylenol	Tablet	Pseudoephedrine 30 mg	Chlorpheniramine 2 mg	Acetaminophen 325 mg	Dextromethorphan 15 mg
6. Dristan	Time capsule	Phenylephrine 20 mg	Chlorpheniramine 4 mg		
7. Sinutab	Tablet	Phenylpropanolamine 25 mg	Phenyltoloxamine 22 mg	Acetaminophen 325 mg	
8. Sudgfed	Tablet	Pseudoephedrine 30 mg			
9. Sudafed Plus	Tablet	Pseudoephedrine 60 mg	Chlorpheniramine 4 mg		
10. 4-Way Cold	Tablet	Phenylephrine 12.5 mg	Chlorpheniramine 2 mg	Aspirin 324 mg	

COMMON NASAL SPRAYS

Product	Form	Decongestant	Other
1. Afrin	Nasal spray	Oxymetazoline 0.05%	
	Nose drops		
2. Alconefrin	Nose drops	Phenylephrine	
3. Coricidin	Nasal spray	Phenylephrine 0.5%	
4. Dristan	Nasal spray	Phenylephrine 0.5%	Pheniramine 0.2%
5. Duration	Nasal spray		
	Nose drops	Oxymetazoline 0.05%	
6. Neo-Synephrine	Nasal spray	Phenylephrine (spray — 0.25 and 0.5%) (drops — 0.125, 0.25, 0.5 and 1%)	
	Nose drops		
7. NTZ	Nasal spray		
	Nose drops	Phenylephrine 0.5%	Theridamine 0.1%
8. Privine	Nasal spray		
	Nose drops	Naphazoline 0.05%	
9. Sinutab	Nasal spray	Xylometazoline 0.1%	
10. 4-Way	Nasal spray	Phenylephrine 0.05%	Pyrimamine 0.2%
		Naphazoline 0.05%	

of swollen mucous membranes. This decreases nasal stuffiness and improves sinus drainage. Decongestants are administered either orally or topically as nasal sprays or drops. The oral decongestants include ephedrine, pseudoephedrine, phenylephrine and phenylpropanolamine. Decongestants used in nasal sprays or drops include phenylephrine, naphazoline, oxymetazoline and xylometazoline.

There is little information available discussing the effects of decongestants on an infant when used by a breast-feeding woman. One case has been documented of an adverse effect from pseudoephedrine. A three-month-old infant exhibited signs of irritability, excessive crying and disturbed sleep after the child's mother had taken a sustained-action

pseudoephedrine product for 1-2 days. The symptoms resolved 12 hours after she discontinued the medication. It is hard to say if the symptoms resulted from the use of a long-acting product or if pseudoephedrine would cause the effect regardless of dosage form.

Phenylephrine is thought to be safe either orally or as a nasal spray. When taken orally, a large amount of drug is destroyed in the stomach without being absorbed. Any phenylephrine absorbed into the body either orally or nasally is broken down or metabolized quickly. Therefore, phenylephrine is believed to be of minimal risk.³

There is no information available regarding the other decongestant medications. The safest one appears to be phenylephrine, but most oral

forms are combined with antihistamines. Nasal sprays containing only phenylephrine are available (Neo-Synephrine, Coricidin and others) and these may be the safest form of decongestant therapy.

Cough is often an irritating symptom of the cold. Coughs are usually classified as productive, one removing accumulated phlegm from the respiratory tract, or nonproductive, a dry noncongested cough.

A productive cough is treated with expectorants which are formulated to decrease sputum viscosity. This eases the expectoration or removal of the phlegm from the respiratory tract by the cough. Expectorants are believed to work by stimulating secretions of respiratory tract mucous glands which decrease the viscosity of accumulated phlegm. This is be-

COMMON COUGH MEDICATIONS

Product	Cough Suppressant	Expectorant	Other
1. Benlyn	diphenhydramine 2.5 mg/ml		alcohol 5%
2. Cheracol	codeine 2 mg/ml	guaifenesin 20 mg/ml	alcohol 3%
3. Cheracol D	dextromethorphan 2 mg/ml	guaifenesin 20 mg/ml	alcohol 3%
4. 2/G		guaifenesin 20 mg/ml	alcohol 3.5%
5. 2/G-DM	dextromethorphan 3 mg/ml	guaifenesin 20 mg/ml	alcohol 5%
6. Novahistine Cough and Cold	dextromethorphan 2 mg/ml		pseudoephedrine 6 mg/ml chlorpheniramine 0.4 mg/ml alcohol 5%
7. Novahistine Expectorant	codeine 2 mg/ml	guaifenesin 20 mg/ml	phenylpropanolamine 3.75 mg chlorpheniramine 0.4 mg/ml alcohol 7.5%
8. Robitussin		guaifenesin 20 mg/ml	alcohol 3.5%
9. Robitussin AC	codeine 2 mg/ml	guaifenesin 20 mg/ml	alcohol 3.5%
10. Robitussin DM	dextromethorphan 3 mg/ml	guaifenesin 20 mg/ml	alcohol 1.4%

lieved to result from a direct stimulus to the glands or a reflex reaction from irritating the gastrointestinal tract.

There is little evidence available supporting the efficacy of expectorants, but they continue to be widely used. Guaiifenesin is an expectorant excreted in the breast milk in small quantities with no effect expected on the infant. Most other expectorants potentially have a deleterious effect on the infant and their use is not recommended.

A nonproductive cough is annoying to the patient as well as irritating to the throat. Since this irritation perpetuates the cough, a patient should try a cough suppressant. The two most popular cough suppressants are dextromethorphan and codeine. These drugs work by depressing the cough center which triggers the cough.

No information is available regarding dextromethorphan excretion in breast milk. Though it is not ex-

pected to cause a problem if used in judicious doses, a definite answer cannot be given at this time. Normal doses of codeine are excreted in breast milk, but in quantities insufficient to affect the infant.³⁻⁵

Headache and a feeling of feverishness (though seldom actual fever) are frequent complaints of the common cold. Both symptoms are effectively treated with aspirin or acetaminophen (Tylenol, Datril and others). Small quantities of aspirin are excreted in breast milk, and there is a slight possibility that aspirin could increase bruising or bleeding tendencies in the infant. An occasional dose of aspirin taken after breast feeding is felt to be safe with a healthy infant. Acetaminophen in normal doses is also felt to be safe, when the breast feeding infant is healthy and has normal liver functions.^{4, 5}

Unfortunately, when discussing cold medications and the breast-

feeding mother, there are no simple answers. Each person must look at the available information, and weigh the possible side effects and risks to the infant against the benefits sought from treatment. Above all, consult with a physician or pharmacist before taking any medication when breast feeding.

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AIDS and Blood Transfusions

What follows is a joint statement on directed donations of blood, a new practice that has evolved as a result of fears of contracting AIDS from blood transfusions. The statement comes from the American Red Cross, the American Association of Blood Banks, and the Council of Community Blood Centers.

The current epidemic of acquired immune deficiency syndrome (AIDS) and attendant publicity have led to concerns that AIDS may be transmitted by blood transfusion to persons not in one of the recognized high risk groups. Of 1,601 cases of AIDS reported to the CDC, 94 percent have occurred in people belonging to four groups: homosexual or bisexual males with multiple sex partners; intravenous drug abusers; recent entrants from Haiti; and persons with hemophilia. Only one newborn infant and 14 adult recipients of blood transfusions have been identified as cases of possible transfusion-associated AIDS. More than 10 million persons were transfused in the United States during the three-year period that these cases were reported and, therefore, it appears at this time that the risk of possible transfusion-associated AIDS is on the order of one case per million patients transfused.

On March 25, 1983, in response to the potential risk of transfusion-associated AIDS, we pledged compliance with the Recommendations on AIDS by the Office of Biologics, FDA, and jointly implemented a nationwide program to inform all blood donors of AIDS risk groups and provided means for individuals in high risk groups to be excluded as blood donors. We concur with Secretary of Health and Human Services Margaret M. Heckler's statement of June 14, 1983, that "... all of us might also be confronted with an un-

necessary and unjustified level of fear, if misunderstanding of AIDS is allowed to grow. Such a level of fear could actually impede us in our real tasks. ..."

One consequence of the understandable, but excessive, concern for transfusion-associated AIDS has been requests by patients and their physicians to have blood donors selected from family members, friends, coworkers, and even newly formed private donor clubs. There is no evidence to support this notion that these "directed donations" are safer than those available through the community blood bank.

The concept that family members, friends, coworkers, church members or other selected groups are sure to provide safer blood is unrealistic. These same individuals are and have been the nation's volunteer blood donors who have, in the past, given freely for all patients rather than for a particular individual. There is no reason to think that segregating these individuals into selected donor panels will provide safety over and above the level provided by current arrangements. In addition, a system of directed donation may create intense pressures on family and friends who may therefore be untruthful about their ability to meet donor requirements. It is possible that the administrative and operational complexity that will be part of any widespread application of directed donations may lead to a significant increase in clerical errors and, in this way, reduce the safety of transfusion.

Finally, there is the risk that widespread attempts to direct donations, while not increasing the safety of transfusions, will seriously disrupt the nation's blood donor system. Voluntary donation is essential for meeting our nation's needs for blood and blood products. There is a real

concern that donors may refrain from routine blood donations while awaiting requests to provide directed donations and, thereby, could disrupt the blood supply to the point that routine and even some emergency needs for transfusions may go unmet.

Given these considerations, we strongly recommend that "directed donation" programs not be conducted. We reaffirm our commitment to a safe blood supply for all recipients, to maintaining the highest standards possible for selecting volunteer donors, and to strict compliance with pertinent recommendations by the United States Public Health Service and other federal regulatory bodies.

The American Red Cross Carolinas Region has issued the following information about AIDS and blood transfusions in North and South Carolina.

The appearance and increase of cases of Acquired Immune Deficiency Syndrome (AIDS) have impressed people and all types of media, creating an atmosphere of fear.

There were 2259 reported cases of AIDS as of September 2, 1983. Over 71% of the cases occur in male homosexuals with a great majority in New York and San Francisco. Intravenous drug users who share needles are the second population involved, and heterosexual Haitians represent the third group. Transmission seems to be NOT CASUAL but by intimate sexual contact.

Blood related cases are suspected in intravenous drug users; about 1% of the cases are hemophiliacs who used lyophilized antihemophilic factor concentrates (population pool up to 20,000 donors) and in lesser degree cryoprecipitate (one donor per

bag used — approximately 100 units). There is only one blood related example in a premature baby in San Francisco, California, who was transfused with platelets from a donor who later developed and died of AIDS. Red blood cells of the same donor were transfused to a patient with terminal leukemia who also died shortly without developing AIDS. Incubation time of AIDS seems to be long (up to 20 or more months). The baby mentioned above also died apparently with AIDS suspected symptoms. About 12 million units of blood are transfused per year in U.S.A. The possibilities are 1 in a million in the so-called "Transfusion Related" cases.

The Office of Biologics of the FDA has specifically recommended measures to blood collection agencies to screen and prevent the possibility of recruiting the so-called "high risk groups" among blood donors. The Red Cross follows those recommendations very strictly. We believe that our blood/blood products are safe and follow all requirements of the OoB.

There have been 12 cases of AIDS reported in North Carolina and South Carolina. Seven were homosexuals coming from New York. Six have died. Five cases were out-of-state residents treated in North Carolina. Figures are not very precise yet.

No screening tests are available. Warning symptoms include severe night sweats, unexplained fevers, unexpected weight loss, swollen glands, or Kaposi's Sarcoma (a rare cancer).

The fear of acquiring AIDS through blood/blood products may cause prospective elective surgery patients to request predonations of their own blood for later transfusions and/or to

consider directed donations (recruiting of blood donors among family or known volunteers). Currently our position is as follows.

Autologous Transfusions: The Regional Director of the Blood Services in consultation with the Regional Medical Advisory Committee has agreed to participate in an autologous transfusion program. Four groups of patients are automatically accepted: patients whose very rare blood types are not available in the inventory of the ARC Rare Donor Registry; patients in whom compatible red blood cells cannot be obtained due to antibody problems; patients whose religious beliefs do not permit blood transfusions from others; very specific prevention of immunization (transplants).

The Regional Medical Advisory Committee recommends that elective surgery patients for plastic surgery and orthopedic patients as well as other special cases be accepted on a one-to-one basis until the magnitude of the demand overpasses actual medico-technical possibilities.

The Medical Advisory Committee will continue to monitor the situation. In the event that the demand for autologous transfusions begins to adversely affect the region's capabilities, new regulations would be considered.

Directed Donations: Concern for transfusion-associated AIDS has led to requests by patients and/or their physicians to have family members and other selected individuals provide blood donations designated for specific recipients. The American Red Cross, together with the American Association of Blood Banks and the Council for Community Blood Centers, strongly recommends that such directed donation programs not be

conducted because: there is no evidence to support the notion that these donations are safer than voluntary blood donations presently available; directed donations create pressures on family and friends who may be untruthful in providing health histories in order to maintain confidentiality of personal information; widespread attempts to direct donations could seriously disrupt the nation's blood supply, as needed donors refrain from giving while awaiting requests to donate for family and friends.

Specific Situations: In certain other situations, family members or unrelated individuals may be selected on a scientific basis to donate for a specific recipient. To clarify why these "donor-specific" matches are not regarded to be "donor directed" the following definitions are provided:

Donor-specific Blood Transfusions. Blood donations may be recruited from a designated living kidney donor, usually a sibling or other relative, for transfusion to the intended transplant recipient. Such transfusions benefit the recipient by improving transplant survival.

Phenotype-Matched Transfusions: Red blood cell, platelet or granulocyte donors may be selected by phenotype from family members or unrelated donors for transfusions to alloimmunized recipients. Such immunologic matching benefits recipients by improving the effectiveness of transfusions.

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Raynaud's Syndrome

Claude S. Burton, M.D., Peter W. Heald, M.D., and J. Lamar Callaway, M.D.

Cold weather induces many changes in our bodies in an attempt to conserve energy. Some of these protective reflexes are exaggerated in an unfortunate few, producing a drastic reduction in blood flow to the hands and, in some cases, the feet. Rarely, parts of the face (nose, ears, chin, cheeks) are affected. This phenomenon has been with us for centuries but was described in the 1800's by Dr. Raynaud and therefore carries his name. The dramatic change in the color of the skin (white to purple when blood flow is inadequate, red during the increased flow of the recovery phase) and the ability to reproduce the phenomenon with cold and other stimuli (emotion, vibration) makes the condition highly recognizable. Raynaud's phenomenon commonly occurs alone but may be associated with serious underlying disease. A careful physical examination and skilled review of systems (asking questions of the patient in order to screen for malfunction of any body system) is recommended for all patients with this disorder to rule out other diagnoses. The management of Raynaud's syndrome embraces many modalities including local, systemic, physical, and psychiatric therapies. Skillfully blending these options with the patient's individual characteristics involves the art of medicine.

The first stage in managing Raynaud's syndrome is to remove or control factors that can produce or aggravate the condition. Repetitive trauma to the hands such as typing or jackhammer work is one stimulus that must be controlled. Smoking must be curtailed to improve circula-

tion. Medications such as birth control pills, propranolol, and bleomycin can exacerbate Raynaud's syndrome and need to be replaced if possible. Since all Raynaud's syndrome sufferers get worse with cold exposure, this also needs to be minimized. Gloves should be kept near the refrigerator to be used for removing cold items. Packet warmers and electric socks are inexpensive aids for the patient who ventures out of doors. Some patients have found it useful to swing the arms about in a windmill-like pattern to force blood out into the hands. This is particularly helpful when an attack of Raynaud's syndrome is beginning.

If additional therapy is needed, there are topical and systemic medications which act on various components of the circulatory system to improve blood flow. The easiest to use are the topical nitroglycerin ointments developed for patients with angina. These can be applied topically to the affected areas to induce blood vessel dilation and thereby increase blood flow. As in angina there is a systemic effect and doses identical to angina therapy are utilized. Systemic blood vessel dilating agents have a long history in the management of the Raynaud's syndrome. If the patient has high blood pressure these are useful; otherwise the side effects of lowered blood pressure and fluid retention (often requiring diuretics) are disconcerting. Medications utilized include nifedipine, guanethidine, reserpine, methyl dopa, prazosin, terbutaline, and phenoxybenzamine. Intraarterial reserpine injection may be useful in managing an acute attack as it reliably produces

local vasodilation and warmth.

Another approach is to decrease the stickiness of the blood. This can be accomplished by inhibitors of platelet aggregation: aspirin, persantine, and intravenous dextran. Since elevated fibrinogen levels can cause the blood to sludge, there are treatments designed to lower the level of this protein in the blood. Various male hormones will accomplish the same thing but with side effects that include facial hair growth, deepening voice, and fluid retention. Some physicians use cobra snake venom (Ancrod) to deplete the excessive fibrinogen. The practice of medicine takes on shades of the old snake-oil vendors with this form of treatment.

The autonomic nervous system controls the muscle tone in the blood vessels of the hands. There are two approaches other than medication that take advantage of this knowledge. The simplest of these is biofeedback. With proper training patients can use programmed relaxation to increase the temperature and blood flow of their hands. Unless there is considerable motivation this program will fail. A second approach is surgical destruction of the nerves running down to the blood vessels of the extremities. This can be done on a trial basis with the injection of a long acting, nerve blocking drug. If the trial is successful, surgery can be offered with similar results.

By reviewing the plethora of methods available for Raynaud's syndrome the clinician can blend the unique features of each patient with those of the treatments and develop a successful therapeutic program.



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The Sarcoid Granuloma as an Immune Endocrine Organ

Nortin M. Hadler, M.D.

No organism has a risk-free niche. Barriers such as skin, the mucociliary mechanisms of the airway, even tears provide some protection from external insults. Since early in phylogeny, and perhaps prerequisite to evolution, complex organisms have evolved mechanisms to compensate for the imperfections in the function of every barrier. These compensatory mechanisms are the immune system. Should an insult breach the barrier, the immune system can recognize the event, neutralize its toxicity and dispose of the insult.

In the simplest form of host defense mechanism, a foreign material breaches the host barrier defense and comes to reside in the extracellular space (where most immune responses occur). Also present in the extracellular space is a heterogeneous population of motile phagocytic cells, the macrophages. By virtue of size or charge or shape or ability to order proteins in the extracellular space, the material is recognized as foreign by a macrophage walking over its surface. That interaction leads to phagocytosis, followed by digestion and disposal.

We have evolved mechanisms that elaborate on this basic scheme, rendering it more sensitive and efficient. We can recognize a substance even if it lacks the inherent physicochemical structure to directly provoke phagocytosis. Each of us has inherited a library of stereochemical conformations or shapes that we are to recognize as foreign. This genetic library is represented in the extracellular space by a population of antibody molecules bearing binding sites, each specific for a particular shape. Should the material breaching the barrier defenses display such a shape, the resident antibody will bind it. That is a recognition event and by itself never leads to disposal. However, a series of these specific antibodies binding the particular shapes on the foreign materials creates a new surface, i.e., a display of ordered Fc regions. The motile macrophages have receptors for such ordered Fc regions and interaction leads to phagocytosis of the antibodies and the material to which they are bound. These ordered Fc coats also have the potential to activate a number of the inflammatory mediator sequences available in the extracellular space such as the complement pathways, the clotting pathway and kinins. Activation releases small peptide fragments with such biological activities as ordering phagocyte motion (chemo-

taxis), increasing vascular permeability, etc. The inflammatory mediators amplify the basic immune sequence by making it more likely that the motile macrophage will encounter the Fc-coated material and dispose of it.

This system has yet another mantle of sophistication illustrated in figure 1. The quantity and nature of antibody molecules present in the extra-cellular space can be varied so that when a particular shape on a foreign substance, X, is recognized, further appropriate antibodies can be synthe-

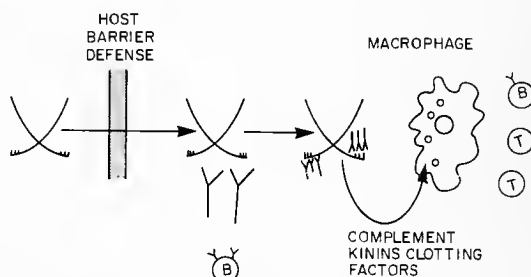


Figure 1. Illustration of the basic element of immune defense. Assume a foreign material, X, breaches the host barrier defense. If X has a particular surface structure in the extracellular space, it will be phagocytized when encountered by happenstance by a motile or resident macrophage. In this figure, the capacity of the immune system to recognize an X with a more subtle structure is depicted. This X displays a structural configuration (antigenic shape) that the host is genetically prepared to recognize. The genetic potential is manifest in the extracellular space by antibody molecules (illustrated as Y) with binding sites specific for the shapes on X. By virtue of specifically binding to X, the surface of X becomes an ordered display of antibody tails (Fc portions). The macrophage has receptors for such an array and phagocytosis ensues. Furthermore this ordered Fc surface can activate complement, coagulation pathways and kinins creating an inflammatory milieu which enhances the efficiency of the disposal of X.

The immune system also has the capacity to process the signal that an X is present and respond with up- or down-regulation. This is accomplished by the formation of a specific immune organ in situ. The macrophage not only disposes of X, but translates the disposal event into a specific communication. (We don't know how, but it can!) B lymphocytes and T lymphocytes aggregate because they have specific receptors for the antigens involved. Depending on the particular population of lymphocytes assembled, the disposal mechanism can be enhanced, suppressed or caused to change direction. The rules that govern the assembly of a particular immune organ are the focus of intense investigation. Cellular surface structures are involved, including histocompatibility antigens. So is the prior immune history of the host.

From the Departments of Medicine and Microbiology, University of North Carolina School of Medicine, Chapel Hill 27514.

Based on a presentation at the Second UNC Symposium on Sarcoidosis, Asheville, North Carolina, October 7-9, 1983.

sized. In part this is accomplished locally by one of the populations of lymphocytes, the B cells, which bear on their surface membrane the particular immunoglobulin the B cell synthesizes. For some antigens, particularly carbohydrates (including lipopolysaccharides), specific B cells can be directly stimulated *in situ*. But the macrophage has a role in this processing as well. Not only can it digest and degrade the phagocytized X, but it can translate the disposal event into an information processing event. The macrophage, digesting this immune complex, becomes "activated." Some activated macrophages serve an accessory function in the stimulation of specific B cells to produce antibody. Some are particularly effective in stimulating T cells by means of secreting a lymphokine such as interleukin-1. There are many varieties of T cells. Some, when specifically stimulated, can help enhance the response of the B cell. Some can interact with X directly. (For example, there are some forms of T cells that are able to kill living cellular targets and even modify viral antigens.) And finally there are varieties of T cells that appear to have principally a modulating role in that they can turn off or turn down certain components of a specific immune response. All of this complexity is occurring *in situ*, in the extracellular space, in the presence of the noxious X.

Essentially an "immune organ" is established at the site of intrusion of the barrier defense mechanism. This immune organ is carefully modulated and designed to specifically dispose of the intruding foreign material. I call it an "organ" because it represents the careful orchestration of intercellular reactions among several components of the immune system including various types of lymphocytes and macrophages. They must all work together. Certain components probably fit together in order to function efficiently. Part of this efficient interaction is specific to the particular X but surface molecules other than antigen receptors interact in forming the immune organ. For example, these cells need to be matched as regards histocompatibility antigen to function efficiently. Of course that is not an issue in a given host (where all cells are matched) but it underlies the insights we are seeking when we attempt to discern an association between a particular histocompatibility antigen and a particular disease state. There are individual differences in surface glycoproteins on many cells including the cells that will form the immune organ. Since these surface molecules are involved in the fine structure of the immune organs, individual differences may lead to differences in the function that results from these cellular interactions.

All of this is health! What can go awry to cause sarcoidosis?

1. What would happen if X were indigestible, i.e. non-biodegradable! For some relatively inert materials such as a bentonite bead or a talc particle, the macrophage attempts or even accomplishes phagocytosis but digestion is impossible. What follows is the next clue to the sophistication of the macrophage as a pivotal cell in the formation of an immune organ. The presence of this non-degradable material in the phagolysosome causes the cell to recruit other macrophages presumably by producing chemotactic substances. There results, about this non-degradable particulate material, a rim of macrophage-like cells that we term a granuloma. For many such insults this response is not

particularly aggressive and may well underlie the few granuloma that all of us have in our spleens and liver.

2. Sometimes the sequence just outlined is observed to be a bit more aggressive. For example if the bentonite bead is coated with antigen and allowed access to the pulmonary bed or liver of an animal that has previously been immunized with that antigen then a larger, more impressive, more cellular granuloma is seen to form.¹ Furthermore the cellular components are far more varied including cells that appear to be macrophages and others that clearly are in the lymphocyte line. Since the material is essentially nondisposable, there results a granuloma but again there need not be major destruction or even illness.

3. But there are circumstances where this scenario is not at all benign. Take the example of inhalation of silica particles that breach the barrier defenses of the alveoli. Silica particles are non-biodegradable and also toxic to cells. In the extracellular fluid they are protein-coated and phagocytized. Once inside the macrophage the protein coating is digested but the particle remains and literally destroys the macrophage from within.² A similar sequence of events occurs with crystals of monosodium urate. In both the silica story and the urate story granulomas form in the extracellular space. In the case of silica the granulomatous response is not well modulated and an interesting turn of events follows: namely, these damaged and dying macrophages put out factors that recruit additional macrophages as well as recruit fibroblasts and even stimulate them.^{3, 4} A fibrosing granulomatous process occurs. The urate granuloma is equally impressive although the form of pathology is different. Here the macrophages produce communicating molecules that commandeer other cells in the ground substance. Interleukin-1 can stimulate catabolic processes by chondrocytes and in concert with osteoclast activating factor (OAF) can provoke an expanding lesion of bone and cartilage destruction we call a tophus.

4. The non-biodegradable substances capable of producing granulomatous inflammation are not that rare. Silica and urate are two examples. The microbial world is replete with such materials.⁵ Notably, bacterial cell walls from particular species can provoke chronic granulomatous inflammation. Depending on the animal and the particular bacterium from which the wall was isolated as well as the form of the wall, one can use non-degradable bacterial cell wall peptidoglycan-polysaccharide fragments to provoke chronic granulation tissue in the heart, or skin, or liver, or even joints.⁶

5. Finally "non-biodegradability" may be more subtle than the physical construct postulated for the examples cited above. Berylliosis is an example of a systemic granulomatous disease with many features in common with sarcoidosis. Here the beryllium is thought to modify endogenous proteins throughout the body creating foci that appear to behave as if non-biodegradable particulate material was present.⁷ Zirconium granulomata that plagued some individuals using zirconium-containing underarm deodorants was probably the result of a similar mechanism.⁸ Although modification of endogenous proteins to create moieties that behave as if they are non-biodegradable is certainly possible, for me it is more appealing to think of sarcoidosis in the light of the previous examples.

Experimental immunology appears to be on the verge of answering the critical questions related to the pathogenesis of sarcoidosis. We need to determine what "non-biodegradable" material is in the center of all these granulomas. Perhaps more importantly, we need to understand how granulomas are modulated (in the sense of the schema in figure 1). The "activated macrophages" that comprise the sarcoid granuloma wherever they are found seem to be displaying an array of functions beyond just attempting to dispose of the putative non-degradable material. They are recruiting and stimulating fibroblasts; witness the pulmonary and myocardial fibrosis. In bone they are activating osteoclasts to produce the characteristic lytic lesions. They produce a family of molecules called Interleukin-1 which not only activates T cells but functions as the long sought "leukocyte pyrogen."⁹ They develop the potential to participate in vitamin D metabolism; this function may explain the hypercalcemia of sarcoidosis and the observation that hypercalcemia can persist in an anephric sarcoid patient.¹⁰ Activated macrophages synthesize and boldly secrete an abundance of enzymes and other proteins¹¹ such as complement components, proteases, lysozyme, and angiotensin converting enzyme.¹² The sarcoid granuloma is indeed an immune endocrine organ, an integrated heterogeneous grouping of cells producing a myriad of factors that influence each other's function and that of cells residing near and far. If we understood these endocrine processes, we

might be able to teach the host to be less aggressive in the granulomatous response; clearly normal tissue is paying the price we call sarcoidosis.

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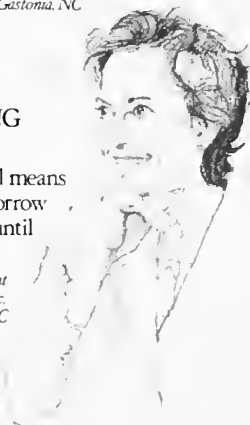
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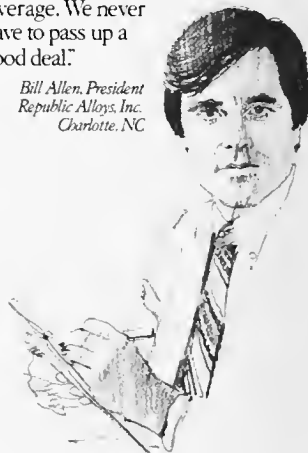
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Things I Know and Things I Don't Know: How to Develop a Better Opinion

David L. Simel, M.D.

WHEN I ask for help from a colleague, sometimes I want facts and sometimes I want opinions. However, I always want my consultant's opinions to have roots in facts. Since opinions are only educated guesses I am more inclined to believe one truth than many half-truths.

A consulting internist's opinion was that my patient with unilateral leg swelling, pain, tenderness, and a Homan's sign had thrombophlebitis. I concurred and was pleased we agreed since his opinion was based on more experience than mine; experience should make us wiser. We learned a truth when the radiologist discovered occlusive iliac vein disease by venography. My guess that thrombophlebitis existed was only based on my youthful experience, not facts. A factual opinion would have required knowing the correlation between symptoms, signs, and disease, not from the untested experience of wiser physicians, but from the published facts of controlled clinical trials. When I force myself to learn facts I can develop better opinions, ask better questions, and learn more from my own anecdotes. If I do not learn to separate truths from half-truths I deceive myself by thinking I know what I really do not.

I was recently asked whether or not to give a young lady streptokinase for deep venous thrombosis. My opinion was yes, but I could not support it with facts. She did quite well receiving fibrinolytic therapy; perhaps she and I were lucky. I subsequently read the literature which compares streptokinase to heparin. Eight weeks later (acquiring facts to develop opinions cannot always be done quickly) I learned what is known about venous thrombi and the clinical use of streptokinase. More important, I know what I do not know and I can ask intelligent questions to those who say they do.

I reviewed about three-dozen clinical studies (no case reports) that used fibrinolytic therapy for deep venous thrombosis. Using a method taught by others I critically appraised each article for certain criteria (table 1).¹ I looked for studies that had specific inclusion and exclusion criteria reflecting what I see in my patient population. The diagnosis had to be confirmed by venogram so that the therapeutic benefit could be attributed to treatment of definite disease. Since I wanted a comparison between two therapeutic modalities, I expected 1) the patients to be successfully randomized to heparin or streptokinase, 2) the treatment method specified in enough detail that I could reproduce it in my own patients, and 3) blinded treatment administra-

Table 1
Criteria for Critical Appraisals

1. Patient selection criteria
2. Diagnostic criteria
3. Prognostic stratification
4. Therapeutic maneuver
5. Blind treatment administration
6. Verification of potential therapeutic benefit by plasma assays
7. Patient allocation method
8. Outcome criteria
9. Blinded outcome assessment
10. Appropriate follow-up period
11. Statistical method

tion and outcome assessment so that I knew the results were not biased. The follow-up period had to be long enough to be clinically meaningful. I committed my appraisals to paper so that my thoughts would be retrievable. Very few studies came close to meeting my requirements for a good clinical investigation; but there was always something useful in the act of reading poorly designed trials: I learned to recognize truths and half-truths. I was able to accept and modify recent recommendations for the use of thrombolytic therapy. (See tables 2, 3.)

The two studies that came closest to passing my critical appraisal found that streptokinase yielded a clinically normal leg in about three-fourths of patients versus heparin which gave a normal result in only one-third (see table 4). The venographic findings were normal in forty-four percent of patients who received streptokinase, but no patients treated with heparin regained normal venous anatomy. Though another forty-four percent of streptokinase patients had major post-thrombotic venogram changes, none had serious clinical findings. Twelve percent of patients treated with streptokinase had only slight post-thrombotic changes. Two-thirds of the heparin-treated patients had major post-thrombotic venogram changes and one-third had slight changes. Other studies that came close to passing critical appraisal yielded comparable results.^{5, 6}

I developed some opinions: 1) that streptokinase is more likely to give the results I would like for my own legs, but 2) that there must be other determinants in the development of the clinical post-thrombotic state besides complete thrombolysis since some patients with no signs or symptoms will have an abnormal venogram years later. I think that there is a greater tendency to serious hemorrhage from fibrinolytic therapy (perhaps 10-15% for streptokinase versus 5% for heparin) but I do not know that since there is an appreciable

From the Department of Medicine, Duke University Medical Center, Durham 27710.

Table 2
Guidelines for Lytic Therapy

+ venogram → below popliteal only → yes → heparin		
	no	
	above popliteal	
Risk Benefit Analysis		
<i>Absolute Contraindication</i>	<i>Relative</i>	<i>Intangibles</i>
Active bleeding	Pregnancy	Post-thrombotic sequelae
Recent (within 2 months)	Menses	Prior deep venous thrombosis
Cerebrovascular accident	Recent (less than 10 days)	Age
intracranial process	Surgery	Co-morbid illness (e.g., decreased life expectancy)
	Post-partum	Symptoms greater than 7 days
	Organ Biopsy	
	Puncture noncompressible vessels	
	Peptic ulcer disease or history of gastrointestinal hemorrhage	
	Course of streptokinase in past year	
	Recent trauma	
	Blood pressure greater than 200 mm Hg systolic or 110 mm Hg diastolic	
	Recent trauma or cardiopulmonary resuscitation	
	Hemostatic defects (including liver or renal disease)	
	High likelihood of left heart thrombus	
	Endocarditis	

From Sharma GVRK, Cella G, Parisi AF, Sasahara AA: Thrombolytic therapy. NEJM 1982;306:1268-1276.

range of complications reported in these three dozen differently designed and controlled studies. Streptokinase therapy is about five times as expensive as heparin, but the cost of fibrinolytic therapy is certainly not prohibitive.

A patient with recurrent deep venous thrombosis poses therapeutic dilemmas. If the patient had previously been treated with heparin rather than streptokinase, the leg

would probably have had an abnormal venographic appearance if studied prior to the recurrent clot (see table 4). A patient with deep venous thrombosis who already had post-thrombotic sequelae would most likely not receive much benefit from fibrinolytic therapy and I would prescribe anticoagulation. What if the patient with recurrent deep venous thrombosis, whose initial event was treated with heparin, was fortunate enough to be among the one-third of such patients returning to clinical normality (see table 4)? Whatever it was that made such a patient have normal legs despite abnormal anatomy, I would want the legs to be like they were before the recurrent thrombus: fibrinolytic ther-

Table 3
Guidelines for Lytic Therapy

If risk-benefit analysis is acceptable for treatment:

1. Stop heparin if patient already on it
2. Pre-lytic labs: TCT, aPTT, PT, Hct, platelet count. (If patient has been on heparin; fibrinogen, FDP).
3. During Treatment:
 - Blood work during treatment with 22 or 23 g needle
 - Bed rest
 - Pressure dressings
4. Vital signs every four hours
5. Hydrocortisone 100 mg IV before treatment, then po q 12-24 hrs. SK 250,000 μ bolus 30 minutes then 100,000 μ hr \times 72 hrs
6. 3-4 hours after bolus check TCT or aPTT
7. If no change, re-bolus with 250,000 μ and continue the infusion. Recheck TCT or aPTT. If still no response, use urokinase or heparin.
8. Stop treatment at 72 hrs, wait 3-4 hrs and recheck TCT or aPTT. When aPTT 2x control, begin heparin without loading dose.

Abbreviations: SK — Streptokinase, BP — blood pressure, TCT — thrombin clot time, aPTT — activated partial thromboplastin time, PT — prothrombin time, Hct — hematocrit, FDP — fibrin degradation products

From Sharma GVRK, Cella G, Parisi AF, Sasahara AA: Thrombolytic therapy. NEJM 1982;306:1268-1276.

Table 4
Treatment Outcome

	Treatment (Percent)	
	Streptokinase	Heparin
Venogram		
Normal	44%	0%
Slight post-thrombotic changes	12%	33%
Major post-thrombotic changes	44%	67%
Clinical Exam		
Normal	76.5%	33.3%
Moderate Signs edema, varicosities, or pigmentation	23.5%	50%
Serious Signs (leg ulcer)	0%	16.7%

From Arnesen H, Hoiseth A, Ly B: Streptokinase or heparin in the treatment of deep vein thrombosis. Acta Med Scand 1982;211:65-68.

apy is much more likely to restore the pre-existent anatomy than heparin.

I do not believe we are administering fibrinolytic therapy the safest way possible and hope that we will find a way to administer it with fewer complications. An innovative treatment protocol combining intermittent streptokinase with plasminogen suggests that there are better regimens.⁷ If we can maintain the therapeutic efficacy of fibrinolytic agents, keep the cost from appreciably rising, and lower the complication rate even further, choosing between streptokinase and heparin will become easy since fibrinolysis will almost always be preferred.

Though I was specifically interested in developing better opinions about the clinical comparison between streptokinase and heparin, simple osmosis expanded my data bank. I learned about plasminogen and the fibrinolytic system, noninvasive assessment of venous function, hemostatic tests, and the cost of the severe post-thrombotic syndrome. I understand that it must be difficult to formulate a well-designed study, but my opinions will be better now that I am able to recognize what is truth and what is a half-truth.

I hope my consultants do not become frustrated if I ask for the facts supporting their opinions. My own consulting

opinions given to my colleagues can now have an appropriate amount of authority since I will be more aware of what I know and what I don't know. Factual opinions do not have their roots in just clinical experience, but are based on critical appraisals and analytic thought. The next patient receiving streptokinase from me will be under the care of a much smarter physician than that lucky young lady.

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References

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BRIEF SUMMARY

PROCARDIA® (nifedipine) CAPSULES

For Oral Use

INDICATIONS AND USAGE 1. **Vasospastic Angina** PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) a classical pattern of angina at rest accompanied by ST segment elevation; 2) angina or coronary artery spasm provoked by ergonovine; or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina. provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm or when angina is refractory to nitrates and/or adequate doses of beta blockers.

2. **Chronic Stable Angina (Effort-Associated Angina)** PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance but confirmation of sustained effectiveness and evaluation of long term safety in those patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS

Known hypersensitivity reaction to PROCARDIA.

WARNINGS **Excessive Hypotension** Although in most patients, the hypotensive effect of PROCARDIA is modest and well-tolerated, occasional patients have had excessive and/or prolonged hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic anesthetics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, a probable result of increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure Rarely patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS **General Hypotension** Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug Interactions Beta-adrenergic blocking agents. (See Indications and Warnings.) Experience in over 1400 patients in a noncomparative clinical trial has shown no clinically important administration of PROCARDIA and beta blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long acting nitrates. PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianalgesic effectiveness of this combination.

Digoxin. Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digoxin toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digoxinization.

Carcinogenesis, mutagenesis, impairment of fertility. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose.

Pregnancy. Category C. Please see full prescribing information with reference to teratogenicity in rats, embryotoxicity in rats, mice and rabbits, and abnormalities in monkeys.

ADVERSE REACTIONS The most common adverse events include dizziness or light-headedness, peripheral edema, headache, weakness, flushing and tachycardia occurring in about 10% of patients; transient hypotension in about 5%; palpitation in about 2%; and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianalgesic medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, diarrhea, constipation, inflammation, joint stiffness, shakiness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, and sexual difficulties. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

Laboratory Tests Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms. Cholestasis, possibly due to PROCARDIA therapy, has been reported twice in the extensive world literature.

HOW SUPPLIED Each orange, soft gelatin PROCARDIA CAPSULE contains 10 mg of nifedipine. PROCARDIA CAPSULES are supplied in bottles of 100 (NDC 0069-2600-56), 300 (NDC 0069-2600-72), and unit dose (10x10) (NDC 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperature 59 to 77 F (15 to 25 C) in the manufacturer's original container.

More detailed professional information available on request.

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Quotes from an unsolicited letter received by Pfizer from an angina patient. While this patient's experience is representative of many unsolicited comments received, not all patients will respond to Procordia nor will they all respond in the same manner.

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for the varied faces of angina

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- 2) Angina where the clinical presentation suggests a possible vasospastic component
- 3) Chronic stable angina without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or nitrates or who cannot tolerate these agents. In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks' duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

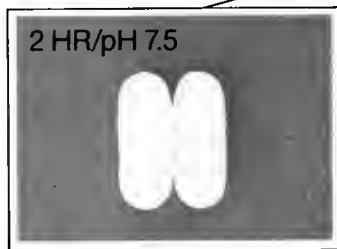
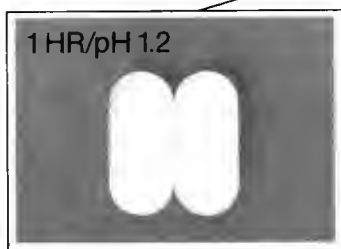
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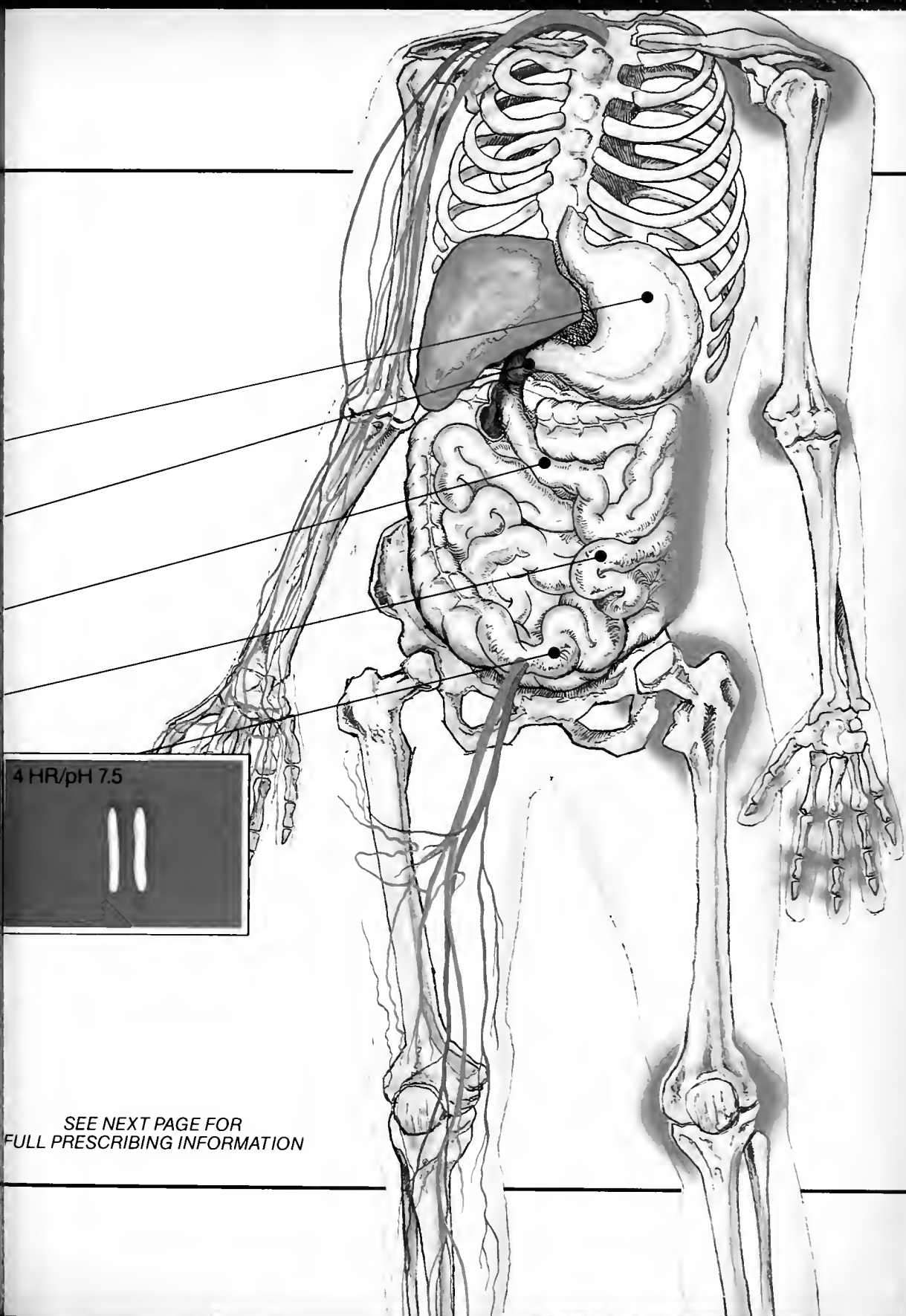
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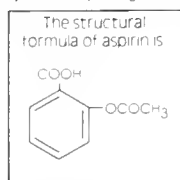


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FULL PRESCRIBING INFORMATION

ZORprin (ASPIRIN) Zero-Order Release

DESCRIPTION: Each capsule-shaped tablet of Zorprin contains 800 mg of aspirin, formulated in a special matrix to control the release of aspirin after ingestion. The controlled availability of aspirin provided by Zorprin approximates zero-order release, the *in vitro* release of aspirin from the tablet matrix is linear and independent of the concentration of the drug. **CLINICAL PHARMACOLOGY:** Aspirin, as contained in Zorprin, is a salicylate that has demonstrated anti-inflammatory and analgesic activity. Its mode of action as an anti-inflammatory and analgesic agent may be due to the inhibition of synthesis of prostaglandins, although its exact mode of action is not known. **Zorprin** is pH-dependent. *In vitro* studies have shown very little aspirin to be released in acidic solutions, whereas, Zorprin releases the majority of its aspirin (90%) in a zero-order mode at a neutral to alkaline pH. It is this pH dependence of Zorprin that reduces direct contact between aspirin and the gastric mucosa, resulting in a reduction of its gastrointestinal side-effect potential. **Bioavailability data for Zorprin** have confirmed that plasma levels of salicylic acid and acetylsalicylic acid can be measured 24 hours after a single oral dose. This substantiates a twice daily dose regimen. Multiple dose bioavailability studies showed similar steady-state salicylate levels for Zorprin as for conventional release aspirin using the same total daily dose. Long-term monitoring of salicylate levels showed no signs of accumulation once steady-state levels were reached (4-6 days). **Studies of *in vivo* prostaglandin levels (PGE₂)** have shown Zorprin plasma levels of salicylic acid and acetylsalicylic acid to reduce PGE₂ levels 14 hours after a single oral 800 mg dose while an equivalent dose of aspirin produced a reduction of PGE₂ levels only through six hours. Zorprin's effect on prostaglandins other than PGE₂ has not been determined. **Salicylates** are excreted mainly by the kidney, and from studies in humans it appears that salicylate is excreted in the urine as free salicylic acid (10%), salicylic acid (75%), salicylic phenolic (10%), acyl glucuronides (5%) and gentisic acid (<1%). **INDICATIONS & USAGE:** Zorprin is indicated for the treatment of rheumatoid arthritis and osteoarthritis. The safety and efficacy of Zorprin have



not been established in those rheumatoid arthritis patients who are designated by the American Rheumatism Association as Functional Class IV (incapacitated largely or wholly bedridden, or confined to wheelchair, little or no self-care). **In patients treated with Zorprin for rheumatoid arthritis and osteoarthritis**, the anti-inflammatory action of Zorprin has been shown by reduction in pain, morning stiffness and disease activity as assessed by both the investigators and patients. **In clinical studies in patients with rheumatoid arthritis and osteoarthritis**, Zorprin has been shown to be comparable to conventional release aspirin in controlling the aforementioned signs and symptoms of disease activity and to be associated with a statistically significant reduction in the milder gastrointestinal side effects (see ADVERSE REACTIONS). Zorprin may be well tolerated in some patients who have had gastrointestinal side effects with conventional release aspirin, but these patients when treated with Zorprin should be carefully followed for signs and symptoms of gastrointestinal bleeding and ulceration. **Since there have been no controlled trials to demonstrate whether or not there is any beneficial effect or harmful interaction with the use of Zorprin in conjunction with other nonsteroidal anti-inflammatory agents (NSAIs)**, the combination cannot be recommended (see Drug Interactions). **Because of its relatively long onset of action, Zorprin is not recommended for antipyresis or for short-term analgesia.** **CONTRAINDICATIONS:** Zorprin should not be used in patients known to be hypersensitive to salicylates or in individuals with the syndrome of nasal polyps, angioedema bronchospastic reactivity to aspirin, renal or hepatic insufficiency, hypoprothrombinemia or other bleeding disorders. Zorprin is not recommended for children under 12 years of age, it is contraindicated in all children with fever accompanied by dehydration. **WARNINGS:** Zorprin should be used with caution when anticoagulants are prescribed concurrently, since aspirin may depress platelet aggregation and increase bleeding time. Large doses of salicylates may have hypoglycemic action and enhance the effect of the oral hypoglycemics, concomitant use therefore is not recommended. However, if such use is necessary, dosage of the hypoglycemic agent must be reduced. The hypoglycemic action of the salicylates may also necessitate adjustment of the insulin requirements of diabetics. **While salicylates in large doses have a uricosuric effect, smaller amounts may reduce water excretion and increase serum uric acid.** **USE IN PREGNANCY:** Aspirin can harm the fetus when administered to pregnant women. Aspirin interferes with maternal and infant hemostasis and may lengthen the duration of pregnancy and parturition. Aspirin has produced teratogenic effects and increases the incidence of stillbirths and neonatal deaths in animals. **If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.** **Aspirin should not be taken during the last 3 months of pregnancy.** **PRECAUTIONS:** Appropriate precautions should be taken in prescribing Zorprin for patients who are known to be sensitive to aspirin or salicylates. Particular care should be used when prescribing this medication for patients with erosive gastritis, peptic ulcer, mild diabetes or gout. **As with all salicylate drugs, caution should be exercised in prescribing Zorprin for those patients with bleeding tendencies or those on anticoagulants.** **In order to avoid exacerbation of disease or adrenal insufficiency**, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when Zorprin is made a part of the treatment program. **Patients receiving large doses of aspirin and/or prolonged therapy may develop mild salicylate intoxication (salicylism)** that may be reversed by dosage reduction. **Salicylates** can produce changes in thyroid function tests. **Salicylates** should be used with caution in patients with severe hepatic damage, preexisting hypoprothrombinemia, Vitamin K deficiency and in those undergoing surgery. **Since aspirin release from Zorprin is pH dependent, it may change in those conditions where the gastric pH has been increased as a result of antacids, gastric secretion inhibitors or surgical procedures.** **Drug Interactions:** (See WARNINGS) Aspirin may interfere with some anticoagulant and antidiabetic drugs. **Drugs which lower serum uric acid by increasing uric acid excretion (uricosurics)** may be antagonized by the concomitant use of aspirin, particularly in doses less than 2.0 grams/day. **Nonsteroidal anti-inflammatory drugs** may be competitively displaced from their albumin binding sites by aspirin. This effect may negate the clinical efficacy of both drugs. **Also, the gastrointestinal inflammatory potential of nonsteroidal anti-inflammatory drugs may be potentiated by aspirin.** The combination of alcohol and aspirin may increase the risk of gastrointestinal bleeding. **Aspirin may enhance the activity of methotrexate and increase its toxicity.** **Sodium excretion produced by spironolactone may be decreased in the presence of salicylates.** Concomitant administration of other anti-inflammatory drugs may increase the risk of gastrointestinal ulceration. **Urinary alkalinizers decrease aspirin's effectiveness by increasing the rate of salicylate renal excretion.** Phenobarbital decreases aspirin's effectiveness by enzyme induction. **Pregnancy Category D.** See WARNINGS Section. **Nursing Mothers:** Salicylates have been detected in the breast milk of nursing mothers. **Because of the potential for serious adverse reactions from aspirin in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the benefit of the drug to the mother.** **ADVERSE REACTIONS: Hematologic:** Aspirin interferes with hemostasis. Patients with a history of blood coagulation defects or receiving anticoagulant drugs or with severe anemia should avoid Zorprin. Aspirin used chronically may cause a persistent iron deficiency anemia. **Gastrointestinal:** Aspirin may potentiate peptic ulcer, and cause stomach distress or heartburn. Aspirin can cause an increase in occult bleeding and in some patients massive gastrointestinal bleeding. However, the greatest release of active drug from Zorprin is designed to occur in the small intestine over a period of time. This has resulted in fewer symptomatic gastrointestinal side effects. **Allergic:** Allergic and anaphylactic reactions have been noted when hypersensitive individuals have taken aspirin. Fatal anaphylactic shock, while not common, has been reported. **Respiratory:** Aspirin intolerance, manifested by exacerbations of bronchospasm and rhinitis, may occur in patients with a history of nasal polyps, asthma, or rhinitis. The mechanism of this intolerance is unknown but may be the result of aspirin-induced shunting of prostaglandin synthesis to the lipoygenase pathway and the liberation of leukotrienes, e.g. slow-reacting substance of anaphylaxis. **Dermatologic:** Hives, rashes, and angioedema may occur, especially in patients suffering from chronic urticaria. **Central Nervous System:** Taken in overdoses, aspirin provides stimulation which may be manifested by tinnitus. Following initial stimulation, depression of the central nervous system may be noted. **Renal:** Aspirin rarely may aggravate chronic kidney disease. **Hepatic:** High doses of aspirin have been reported to produce reversible hepatic dysfunction. **OVERDOSAGE: Overdose, if it occurs, would produce the usual symptoms of salicylism: tinnitus, vertigo, headache, confusion, drowsiness, sweating, hyperventilation, vomiting or diarrhea.** Plasma salicylate levels in adults may range from 50 to 80 mg/dl in the mildly intoxicated patient to 110 to 160 mg/dl in the severely intoxicated patient. An arterial blood pH of 7.1 may indicate serious poisoning. The clearance of salicylates in children is much slower than adults and should receive due consideration when aspirin overdoses occur in infants. Salicylate half-lives of 30 hours have been reported in infants 4-8 months old. Treatment for mild intoxication should include emptying the stomach with an emetic, or gastric lavage with 5% sodium bicarbonate. Individuals suffering from severe intoxication should, in addition, have forced diuresis by intravenous infusions of sodium bicarbonate and dextrose or sodium lactate. In extreme cases, hemodialysis or peritoneal dialysis may be required. **(A plasma salicylate level of 160 mg/dl in an adult is usually considered lethal.)** **DOSEAGE & ADMINISTRATION:** In order to achieve a zero-order release, the tablets of Zorprin should be swallowed intact. **Breaking the tablets or disrupting the structure will alter the release profile of the drug.** It is recommended that Zorprin be taken with sufficient quantities of fluids (8 oz. or more). **Adult Dosage:** For mild to moderate pain associated with rheumatoid arthritis and osteoarthritis, the recommended initial dose of Zorprin is 1600 mg (2-800 mg tablets) twice a day. Because of Zorprin's prolonged release of aspirin into the bloodstream, Zorprin tablets may be taken as a b.i.d. dose. Further adjustment of the dosage should be determined by the physician, based upon the patient's response and needs. Since it will take 4-6 days to reach steady-state levels of salicylic acid with Zorprin, it is recommended dosages be given for at least one week before further adjustment. In general, patients with rheumatoid arthritis seem to require higher doses of Zorprin than do patients with osteoarthritis. **Zorprin is not recommended for children below the age of 12.** **HOW SUPPLIED:** Zorprin Tablets 800 mg; plain white capsule-shaped tablets. **Bottles of 100 Tablets—NDC 0524-0057-01** **Caution:** Federal law prohibits dispensing without prescription. **U.S. Patent No. 4,308,251** **Manufactured and Distributed by: BOOTS PHARMACEUTICALS, INC., Shreveport, Louisiana 71106 U.S.A.**

12-83 0057-04

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Atrial Fibrillation With Long Survival

William Harding Kneedler, M.D. and John J. Guyer, M.D.

ATRIAL fibrillation is common in hearts with a variety of identifiable disease states. At times the presence of atrial fibrillation is the only abnormality indicating that a particular heart is different from what we call a normal heart. While we do not know the reason for the difference, the absence of sinus rhythm informs us that a difference is present. Observation teaches us that in certain instances the structural change accounting for fibrillation is non-progressive and that the prognosis of the patients with this undetectable structural change is different from that present in hearts damaged by known disease processes. Friedberg¹ reported that 5 to 6% of atrial fibrillation occurs in hearts with no other findings. White² said, "Sometimes violent exertion and excitement are responsible for the onset of paroxysmal or permanent atrial fibrillation with little or no heart disease." In some instances, intermittent atrial fibrillation may become permanent.

In some family groups there is a familial tendency. White³ said, "Several members of a family may be affected, even in youth, without serious heart disease, and in fact in some cases without any disease at all." Friedberg¹ reported two brothers and the 28-year-old son of one of them as having recurrent atrial fibrillation with no other evidence of cardiac abnormality.

Atrial fibrillation in the presence of valvular and myocardial diseases lowers the efficiency of the heart as a pump. In their absence, patients with atrial fibrillation may live many years. No studies have been done in this group to measure the efficiency of the fibrillating heart. When the senior author was an intern at the Pennsylvania Hospital, the hospital barber told him that he had had atrial fibrillation continuously for 40 years. He examined him and found the

heart totally irregular. This man died in congestive heart failure about a year later. White reported a case of atrial fibrillation of over 30 years' duration, and one of flutter of over 40 years' duration whom he had followed for 32 years and who had enjoyed constant good health. This woman was 77 and still in good health when he made his report.

The person whose story we wish to report here had atrial fibrillation for more than 60 years during which time he enjoyed good health and never showed any sign or symptoms of heart disease.

Muang Chai Chainilpant of Chiang Mai, Thailand, a medical practitioner, developed total cardiac irregularity while playing badminton in 1905 or 1906 at the age of 20. His heart remained totally irregular thereafter until he died very early in 1968 at the age of 82. Dr. E. C. Cort followed him for many years, considering the condition to be atrial fibrillation. The senior author first checked him in 1931 and followed him through 1941, seeing him again in 1949-51 and during 1967. His heart was always totally irregular. The junior author first saw him in 1957 for irregular heart and hypertension and followed him until his death from a CVA in 1968. No electrocardiograph was available until 1958, at which time ECG showed the typical findings of atrial fibrillation and continued to do so thereafter.

At least three other members of this man's family also have had atrial fibrillation, including a son, a nephew and a niece. The niece, now 53, had intermittent atrial fibrillation for five years followed by permanent atrial fibrillation for the past 15 years.

We believe that this case of atrial fibrillation, with survival for more than 60 years, represents the longest survival with this condition continuously on record.

References

1. Friedberg C: *Disease of the Heart*, 3rd ed., 1966, p. 538.
2. White P: *Heart Disease*, MacMillan, 1951, p. 900.
3. White P: *Hearts, Their Long Followup*, Saunders, 1967.

From 234 Scenic Drive NE, Concord 28025 (Dr. Kneedler) and Chiang Mai, Thailand (Dr. Guyer).

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The State of Medicine in 1912*

J. C. Walton, M.D.

IN the springtime of 1879 two verdant young country medicos might have been seen wending their sad journey to Greensboro to undergo that terrible ordeal, an examination before the State Board of Medical Examiners. The writer will never forget what fear and trembling possessed his soul when first confronting that august body and his unbounded joy and enthusiasm when told that he had passed.

My friend in misery was Dr. Charles E. Bradsher of Person County, North Carolina who later became the leading physician in that section of this State and but for an early death from the great white plague might easily have adorned and graced any position in this honorable body.

Dr. Bradsher was a born physician and the most resourceful one that I have ever known. I recall on one occasion when called to relieve a small boy suffering from retention, the doctor not having a catheter and the case being very urgent, he improvised an instrument from a feather and saved the day. On another occasion when called to see a man who was seriously hurt in a drunken brawl he found a fractured skull and a bad fracture and dislocation of one of the extremities; after raising the depressed bone the patient became conscious and then attempting to relieve the limb the man became so unmanageable that the good doctor depressed the bone on his skull and he became quiet and unconscious, and after dressing the limb the doctor again lifted the fragment off the skull, the man became conscious and made an uneventful recovery. You can readily perceive that no anaesthetic was available and the doctor's ingenuity had to meet the issue. In other words, the man and the occasion met.

From the above you will readily see that the life of the country doctor tends to develop the qualities of resourcefulness and of self-reliance. I know of no better training school for the recent graduate in medicine than five or ten years of country work. It will make a good physician of him, if anything will.

After securing our licenses we were so elated that my friend Bradsher thought that the next thing in order was to have some visiting cards struck off with the honorable distinction thereon: "Member of the State Medical Society," as we were the pioneer Board Tacklers from the respective counties of Person and Caswell, we did not like to hide our light under a bushel, but after a little reflection and time to allow our enthusiasm to cool we reluctantly decided to forgo this honor, lest it might be thought by our friends to savor of charlatanism.

In the olden days the medicos were not afflicted with the

surgery craze but they were taught the most important and useful branches. The ones they would need most in their daily work, viz.: practice of medicine, obstetrics, materia medica, therapeutics, and physical diagnosis as in those days the doctor was required to diagnose and to treat his own patients *secundum artem*, otherwise he would soon find himself in the position of a doctor without a patient.

Per contra — in these modern, up-to-date times every medico is a born surgeon. The good old branches are obsolete and the old family doctor has become a tradition in this age of specialism and agnosticism.

It is considered by many to be an indication of culture to be an unbeliever, a scoffer and a doubter — even the good old family Bible is losing caste and is being relegated from its seat of honor on the center table in our parlors — to the garret.

Should God's last and best gift to man become ill, she visits a specialist, an internal medicine man, who probably has had good laboratory facilities, but lacks clinical experience and the saving grace of common sense. This gentleman in order to sufficiently impress her of his great and transcendental importance takes down a long clinical history and she gets a gastric, urinary, fecal and blood ex. et al., etc.

For her headaches she is referred to an ophthalmologist, gets a mydriatic and is told to use glasses. For the pain in her abdomen she is sent to the omniscient and omnipotent surgeon who finds that she has appendicitis and that her gallbladder needs draining. Possibly her uterus is slightly displaced, for which she needs a ventral fixation, curettage, etc. After emerging from all this, a shadow in body and mind, the neurologist gets her and she continues the downward route and like the woman mentioned in the Scriptures, suffered much at the hands of many physicians.

Her resources being about exhausted, and likewise having exhausted scientific medicine, like a drowning person she catches at a straw and seeks solace in Christian Science when she is comforted with the good news that there is no such thing as sickness, disease or death.

Gentlemen, are we wholly to blame for this unfortunate state of affairs? If we would cling closely to the ideals of the fathers and always consider the interest of the patient paramount, there undoubtedly would be less of quackery and charlatanism.

We all realize that medical overloading is bad and the more doctors who are called in to see a case the less is the individual interest and responsibility felt by each one of them.

Erichsen taught that a man should be in general practice twenty years before adopting a specialty and in my student days, ten years' general work was considered necessary

* Excerpted from a paper published in the June 19, 1912 *Transactions of the North Carolina Medical Society*.

before specializing. I believe that after graduating, one or two years as an intern in a general hospital followed by two

or three years of country work would sufficiently broaden one's perspective to make him eligible for special work.

THE MORE THINGS CHANGE, THE MORE THEY STAY THE SAME

The State of Medicine in 1983

The Extinction of the Physician

Nortin M. Hadler, M.D.

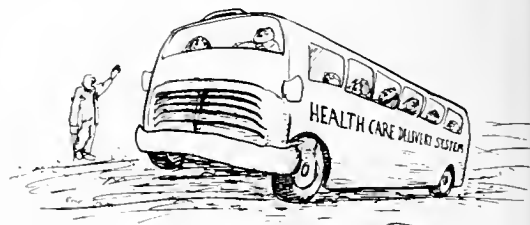
FOR all of us who practice medicine by choice and to the best of our ability, this is a perplexing time, a time of paradox. We have more to offer our individual patients than at any time in the history of medicine, yet society does not seem to champion our role. As I continue to ponder this paradox, I'd like to share some of my perceptions in the hope they are insights.

After World War II, science was ripe for application to medicine and society was ready. Commencing with the Truman administration, federal monies began to flow into the medical schools for the training and sustenance of clinical investigators. For the first time, young doctors with skill, interest, talent, and commitment saw no financial barriers to pursuing a career in investigative medicine. The result was the golden age of clinical investigation which thrived with little distortion into the early 1970s. As a result, we possess a pharmacopoeia brimming with agents that are effective if used appropriately, a technological armamentarium for diagnosis and life support that boggles the mind, and a surgical craft approaching the limits of macroscopic manipulation. The fate of academic departments dedicated to clinical investigation is a tragic spectre upon which I have expounded elsewhere (*De Morte Medicinae, Clinical Research*, February, 1984). More germane to this discussion is the fashion in which they functioned in their heyday.

In these departments and in the medical schools they came to dominate, the clinical investigator assumed preeminence. To test one's inferences relative to the pathophysiology of disease or, secondarily, to its treatment, was clearly the highest calling to which a physician could aspire. Throughout the fabric of Western medicine, there is no argument against this tenet. Such a role, however, was not only the most laudable pursuit; it was the only pursuit worthy of high praise. The acclaim garnered by previous generations of physicians for their astuteness at the bedside, for their reasoning on behalf of the patient seen one at a time, for their clinical categorizations, and for their compassion and stature was silenced. The physician was now called a "clinician" to distinguish him from the inves-

tigator, was downgraded to second-class citizen in the academy and often vanquished. There was no protest; the accomplishments of the investigative establishment were brilliant, overpowering, and ethical. The clinician had to applaud. He also had to await and exploit every advance that was forthcoming.

These events, largely laudable, carried with them a second agenda. The precedent for expending large sums of federal money on medical education and clinical investigation was set. Simultaneously, the academic establishment let it be known that investigation was their calling, their dream come true. All else in their traditional purview was secondary. The stage was set for the development of an efficient, global, egalitarian means of making the dramatic advances of investigative medicine available and for accomplishing the aspects of patient care considered more mundane. And the stage was set by individuals whose backgrounds and proclivities gravitated toward administration and policy formulation. The "health care delivery system" was born. The size and scope of the "system" is far beyond the richest imagination in 1950. Of course, it infected and converted the medical schools. Our leading institutions prefer to be called "academic health (or medical) centers," conglomerates of many schools, disciplines, hospitals and missions (Lewis IJ, Sheps CG: *The Sick Citadel*, Oelgeschlager, Gunn & Hain, Cambridge, Mass., 1983).



An ill individual may still turn to and value his physician. But in the minds of health care planners, the physician is weighted as simply one resource, option or component. Even the academic medical center doesn't strive to nurture such an individual. Instead, patients are treated to and by a

From the Departments of Medicine and Microbiology, University of North Carolina School of Medicine, Chapel Hill 27514.

Illustrations by Ernest Craige, M.D.

health care delivery system. Doctors themselves are too skilled, too highly trained, and too scientific to be expected to help patients cope with the impact of their disease on their life, with their illness. Doctors are to wield science and technology to treat and occasionally cure diseases, blind in their faith that such an effort will solve their patient's predicament. The system has cultivated minions to supplement the exalted and supposedly time-consuming efforts of the doctor: family nurse practitioners, physician assistants, social workers, a polymorphism of counselors and therapists (occupational, rehabilitation, physical, vocational, recreational, dietary to mention a few) and a burgeoning administrative structure with a life of its own. Perhaps the ultimate in this evolution is the production of less scientifically focused doctors who, admittedly and intentionally, pull back from the cutting edge of scientific medicine. "You can't learn it all, why try?" seems to be their banner. Their selling point, at best, is that they attempt to substitute skill and training in manipulating the impact of the disease on the patient's life; at worst, they offer only failure in manipulating the health care delivery system.

The current establishment speaks with one of two voices:

1. We are living in the golden age of applied science. The horizons are limitless. Scientific medicine will provide answers that will allow most of us to live out our full life expectancy free of morbidity.

2. Taking advantage of the past and future advances of medicine and its allied sciences requires yet a more efficient, more sophisticated and better designed health care delivery system that matches the possible with the feasible.

Of course, there is always a role for doctors; they are necessary to apply the most scientific and technological advances. They are as integral to the system as the medical school is to the academic health center. No one seems to have identified a niche, need or role for a personal physician any more. The system has become the substitute for the individual who is a student of the human predicament bringing to the bedside compassion, perspective, and science as a practitioner of the philosophy that was medicine.

The social realities are such that the process that will lead to the extinction of the physician appears inexorable. To reverse it, or even slow it down, requires cogent rebuttal of the two establishment arguments listed above:

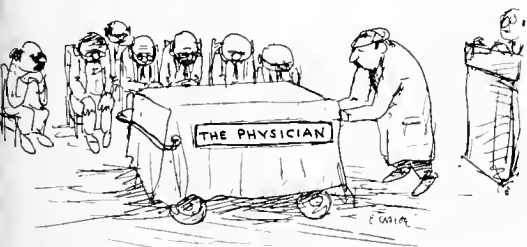
1. Your hope is delusional. There is no technological solution to the human predicament. You may cure a disease

or two but in the experience of illness disease is only one operating variable. The cure of an acute infection, the setting of a fracture, and the suturing of a wound are not particularly demanding undertakings. Consider the judgment necessary to administer a marginal therapy; consider the quandary of a patient with chronic inflammatory disease; consider the impact of the personal experience of any illness on family or in the workplace. Then tell me you see a solution on the horizon of molecular biology.

2. All systems have one serious flaw: they develop their own constituency. There will always be people who commit to the system rather than its output or mission. Making sure that a "health care delivery system" remains an infrastructure is an exercise that has seldom succeeded. Clearly the American system of today appears responsive to the interests and often greed of almost all groups involved. Only the individual patient, the solitary human being who is afraid, anxious, with functional incapacity or even in pain, has no defined advocate. He has no physician.

If American society desires to maintain a cadre of physicians, then there is an immediate need to re-examine the fashion in which we educate the next generation of physicians. The medical schools must be cleaved from the academic health centers and held accountable for the education of physicians and for maintaining the ethical fabric of medicine by example. Clinical departments belong in a medical school and must be excellent. The "basic sciences" are appropriately in the faculty of Arts and Sciences. All Arts and Sciences faculties are relevant to medical education; the universities must become aware of this and faculties learn to share and communicate. Medical students should enter with strong undergraduate grounding in the liberal arts as well as the sciences. Medical school should be a structured 7-year graduate curriculum (almost everyone spends at least 7 years in training anyway, 4 in medical school and 3 postdoctoral years). Exposure to natural and social sciences should be integrated with training in clinical application throughout the 7 years. The faculty should be laced with exemplary physicians teaching and taking many of these courses throughout their careers. The ethic they live is patent: "You can't learn it all, but you never cease trying." After 4 years students can opt for a career in bench science having enjoyed intensive exposure to human biology. After 7 years we will graduate a cohort of physicians all sharing the skills that we'd like to ascribe today to the primary care internist-pediatrician. Individuals who want to master and practice a technology as well (pathology, surgery, invasive procedures, etc.) will require further training. The period required, however, is limited since their education will already have been substantial and the need for perspective well ingrained.

There are many obvious stumbling blocks to such a radical change in medical education, from licensure issues to faculty remuneration. There are even more issues that are imponderable. But if we believe in the goal, all are surmountable. Doctors must be held accountable for their wisdom as physicians. Perhaps if we produce these neighborhood Maimonides, the absurdities of the health care delivery system and industry will become apparent to all and finally remedied. But for now, my elegy is appropriate.



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THE 18-HOUR-A-DAY DOCTOR



Dr. Gaine Cannon

A modern-day version of the country doctor on horseback, Dr. Gaine Cannon covered his scattered practice around the Blue Ridge Mountain country near Balsam Grove, North Carolina, in a four-wheel-drive Jeep wagon.¹

On an average working day, Dr. Cannon rose at sunup to see patients at his converted-farmhouse clinic before setting out to make his usual 15 to 20 house calls around the countryside. Generally, after treating his primary patient, he saw each member of the family, as well—his personal effort at preventive medicine.

Multiple services

With the nearest hospital some 60 miles away and no pharmacy closer than an hour-and-a-half drive, Dr. Cannon filled his own prescriptions, delivered babies

and treated many patients at a centrally located general store with the most modern techniques and medications. After a day on the road—usually within a 50-mile radius—Dr. Cannon's office hours would begin at 5:30 p.m. and stretch on until the last patient was attended to. His record-keeping sessions routinely filled the hour before midnight—rounding off Dr. Cannon's 18-hour day.

At all hours

But emergencies often interrupted his sleep. Dr. Cannon claimed his real office hours were 24 hours a day, and his patients revered him for it.

Dr. Cannon died in 1966 at the age of 68. He will be long remembered—most especially by the more than 5000 North Carolinians he helped bring into the world, some of them at the side of a rutted country road.

Reference: 1. Doctor in the backwoods, in Lee RV, Eimerl S et al. *The Physician*. New York, Life Science Library, Time Inc., 1967, pp 38-50



When the history reveals anxious depression...

For the estimated 70 percent of nonpsychotic depressed patients who are also anxious,¹ Limbitrol provides both amitriptyline, specific for symptoms of depression, and the effects of Librium® (chlordiazepoxide HCl), the tested and dependable anxiolytic. Limbitrol is, therefore, a better choice for these patients than dual agents that contain a phenothiazine, a class of antipsychotic drugs used infrequently in nonpsychotic patients.¹

62% of Overall Improvement...Within the First Week

Limbitrol also has a rapid onset of action which may lead to greater patient compliance. In a multicenter study, patients taking Limbitrol experienced 62% of their overall improvement within the first week of therapy.²

In another multicenter study,³ the following symptoms associated with anxious depression were significantly reduced during the first two weeks of therapy:

- ☐ Headache—79%
- ☐ Early insomnia—91%
- Middle insomnia—87%
- Late insomnia—89%
- ☐ Gastrointestinal upset—73%

In two multicenter studies, only 1.9% of Limbitrol patients experienced cardiovascular side effects.³

Patients should be cautioned about the combined effects with alcohol or other CNS depressants and about activities requiring complete mental alertness such as operating machinery or driving a car.

References: 1. Rickels K: Drug treatment of anxiety, in *Psychopharmacology in the Practice of Medicine*, edited by Jarvik ME; New York, Appleton-Century-Crofts, 1977, p. 316. 2. Feighner JP *et al*: *Psychopharmacology* 61: 217-229, Mar 1979. 3. Data on file, Hoffmann-La Roche Inc., Nutley, NJ.

In moderate depression and anxiety

Limbitrol®

Tablets 5-12.5 each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)
Tablets 10-25 each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt)

Please see summary of product information on following page.

LIMBITROL® TABLETS (Tranquillizer—Antidepressant)

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of moderate to severe depression associated with moderate to severe anxiety

Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use, then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction.

Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

Usage in Pregnancy: Use of minor tranquilizers during the first trimester should always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage, withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline, symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs.

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecostoma in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female and elevation and lowering of blood sugar levels.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

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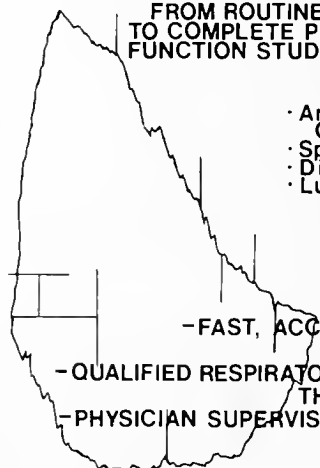
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The Practice of Family Medicine in North Carolina

James G. Jones, M.D., Dennis A. Revicki, Ph.D., and Marianna Tepaske

GENERAL and family physicians provide approximately one-third of the ambulatory medical care in the United States.¹ The specialty of family practice was established in late 1969. Today, a little more than a decade later, family practice is a discipline in evolution. In 1931, eighty-three percent of all private practitioners were family physicians. By 1979 they comprised only 18 percent of physicians delivering patient care.² In the 1970s there was a great proliferation of family practice residency programs resulting in a significant increase in the number of residency-trained family physicians practicing throughout the United States.

The medical practice characteristics and the delivery of medical services by family physicians are of considerable interest since the emerging practice patterns of young family physicians are likely to influence the future content of family practice.³ Marsland,⁴ Curry⁵ and, more recently, Rosenblatt⁶ have investigated the practice characteristics and medical care provided by family physicians. More than ten years ago the clinical content of general practice in North Carolina was investigated.⁷ In this study, the similarities and differences between general practice and other primary care specialties were explored.

These studies were limited by the fact that there were few family practice residency programs in existence and there were only a small number of residency-trained family physicians in practice during the time the data were collected. Therefore, the impact of these physicians on the content and practice of family medicine could not be completely evaluated.

Investigations concerning the practice of family medicine are important. They provide information necessary for the development of residency program curriculum, characteristics of the ambulatory medical care provided by family physicians, and hospital credentialing of family physicians. The objective of the present study was to assess the medical practice activities of family physicians in North Carolina.

Methods

To assess the medical practice activities of family physicians in North Carolina, a 40 question interview schedule was developed. The first section contained items requesting information on general demographics, medical education and postgraduate training, and practice characteristics.

The remaining sections included questions concerning medical care delivery, professional services, and patient population characteristics. The specific questions used in the interview schedule, in addition to those written by the authors, were derived from a number of sources including national and local studies of family practice.⁸

A modified version of the National Ambulatory Medical Care Survey Patient Record⁹ was used to gather specific information regarding a subsample of 150 consecutive patient encounters in each physician's practice. These forms include information on date of service, patient demographic characteristics, reason for visit, medical diagnoses, diagnostic services provided, and the length and disposition of the encounter. The International Classification of Health Problems in Primary Care (second edition) was used to record up to four diagnoses per patient visit.¹⁰

In the spring of 1982, a random sample of the 552 diplomates of the American Board of Family Practice in North Carolina were mailed an invitation to participate in the study. The letter indicated that participation would require a brief interview and the reporting of 150 consecutive patient encounters during the days following the interview. Of the 200 invitation letters mailed out, 88 indicating a willingness to participate were returned, resulting in a response rate of 44 percent. Of these physicians, three were unable to participate in the study for various reasons. Eighty-five family physicians were interviewed and 80 supplied completed encounter forms.

Results

The low response rate raises some question concerning the representativeness of the sample. To evaluate this, the demographic, training and practice characteristics of the respondents in the study sample were compared with data obtained from the NCAFP and other published sources.^{2, 11, 12} The distributions of characteristics in the comparisons were similar, suggesting that the physicians in the study sample were representative of the population of family physicians practicing in North Carolina. The demographic characteristics of the sample were comparable to similar statistics compiled from national studies of family physicians practicing in the Southeast.^{11, 12}

Physician ages ranged from 30 to 68 years, with an average age of 42 years. Of the 85 physicians the majority were male (97%), white (96%), married (96%), and possessed two or more years of post-doctoral training (59%). The average year of graduation from medical school was 1965, with a range of 1941 to 1978.

From the Department of Family Medicine, East Carolina University School of Medicine, Greenville 27834.

Table 1
Practice Location

Community Population	Percentage
Greater than 40,000	16
25,001-40,000	18
10,001-25,000	21
5,000-10,000	21
Less than 5,000	25

In respect to medical practice characteristics, most of the respondents indicated that they were in solo (39%), partnership (22%), or single specialty group practice (25%). Only 13% were in multiple specialty group practices. Most physicians practiced in small cities or towns and rural areas with populations less than 25,000 (see table 1). More than 66% of the practices were located in these areas. Eighteen percent reported practicing in cities with populations between 25,001 and 40,000. The average number of years in practice was 14 for the group, with a range from 1 to 41 years. Significantly, the average number of years in practice at their current location was 12.8 years with a range from 1 to 36. It appears that most of the physicians sampled remained fairly stable in their practice location. The sample physicians reported working an average of 58 hours per week, ranging from 42 to 84 hours per week.

Information on the characteristics of hospitals and hospital privileges of the family physicians included in the study were requested. Ninety-four percent of the physicians were associated with hospitals where they admit patients. Number of hospital beds ranged from 20 to 400, with 59 percent between 100 and 399. For most of the physicians (70%), the hospital was nine or less miles away. About ten percent of the physicians reported that the closest hospital was more than 20 miles. Approximately 93 percent of the family physicians had active full-time hospital staff privileges.

Medical service delivery characteristics are summarized in table 2. An average of 145 patients per week are seen by the family physicians in the sample. Between 100 and 159 patients are seen per week by approximately 58 percent of the physicians. Most patient encounters occur in the office

Table 2
Medical Service Delivery

Patient Office Visits Per Week	Percentage
60-99	8.4
100-129	32.6
130-159	25.3
160-189	20.4
>190	13.3

Practice Settings	Average Hours Per Week	(Range)
Office	40.2	26-60
Hospital	13.8	2-30
Emergency room	4.4	1-25
Nursing home	3.1	2-30
Home	1.7	0-7
Other	3.1	0-8

setting. Physicians reported spending an average of 13.8 hours in the hospital, 4.4 hours in the emergency room, and 3.1 hours in nursing homes. The average number of days between scheduling a nonemergency appointment and the actual appointment was about three days for established patients and four days for new patients. Most of the family physicians interviewed reported that they included pediatrics (95%), emergency care (97%), counseling (97%), and house calls (89%) as part of their medical practice. Approximately 51 percent of the physicians reported providing obstetric services to their patients.

Patient encounter information was requested from all physician offices. In total we received 8854 ambulatory patient encounter forms. Patient demographic characteristics for these encounters are summarized in table 3. Fifty-six percent of the ambulatory encounters are with females. The distribution of race in the sample encounters compares well with statewide distributions. Sixteen percent of family physician office encounters are with infants or children under 14 years of age. Twenty-two percent are with geriatric patients.

Continuity and comprehensiveness of care represent important precepts in the practice of family medicine. Results of the present study indicate that continuity of care is realized for a majority of patients. More than 88 percent of the patients had been seen previously by the physicians and 60 percent had been seen for the same diagnosis. The family physicians sampled provided the majority of care for 83 percent of the patients and 59 percent of these patients' families. Information regarding the patient's major reason for visit are summarized in table 4. Almost twice as many visits occurred for acute problems as for chronic problems. Fifteen percent of the visits were for non-illness care.

Information on various diagnostic services that may be ordered or provided during an office visit were reported. A limited history or examination was performed during 55 percent of all visits. The procedures provided most frequently were blood pressure checks (59%) and clinical laboratory tests (36%). A general history and comprehensive examination occurred during 16% of the visits.

The encounter diagnostic information was summarized using the diagnosis cluster methodology developed by Schneeweiss et al.¹³ The ten most frequent diagnosis clus-

Table 3
Patient Characteristics for Office Encounters

	Percentage (N = 8854)
Sex	
Male	44
Female	56
Race	
White	81
Black	18
Other	1
Age	
<3	6
3-14	10
15-24	14
25-44	26
45-64	23
≥65	22

Table 4
Major Reason for Patient Visit

Reason	Percentage
Acute Problem	52
Chronic Problem	29
Post Surgery or Injury	2
Non-Illness Care	15
Other	2

ters abstracted from the office encounters are reported in table 5. These diagnosis groups account for approximately 53 percent of the collected ambulatory encounters. The most frequent medical problems treated by family physicians in the sample include acute upper respiratory tract infections, hypertension, diabetes mellitus, pre- and post-natal care, and soft tissue injuries. Eleven percent of office visits were for general medical examinations.

Discussion

This study was designed to assess the content and medical practice activities of family physicians in North Carolina. Several important conclusions can be drawn from the results of this study regarding the practice of family medicine in North Carolina.

Certain characteristics that typify the family physician in North Carolina are worth highlighting. The typical family physician is engaged in the delivery of comprehensive front line medical care. Children, women, and elderly patients seek the services of the family physician with great regularity, representing 16%, 56%, and 22%, respectively, of the family physician's ambulatory practice. Family physicians provide a significant portion of the health care for the women in North Carolina. The clinical content of family practice is broad and continues to demonstrate that family physicians serve the entire general population.^{14, 15}

The results of this study indicate that family practice is not just an outpatient, ambulatory care specialty. Family physicians in the sample spent an average of 26 percent of their work time in hospital settings. This replicates the Rosenblatt et al. study⁶ which found that on a national sample 23 percent of the family physicians' encounters occurred in the hospital setting.

There were some findings that might surprise other specialist colleagues. Ninety-seven percent of family physicians regularly include various types of counseling in the

routine service they provide patients. Perhaps most surprising was that 89% of family physician respondents in North Carolina still routinely make house calls.

Of great significance is the apparent change in the direction of family physicians regarding the inclusion of obstetric service in the practice of family medicine. Fifty percent of family physicians in North Carolina surveyed in this study regularly provide obstetrical service to their patients. This is a radical shift in attitude by family physicians from fifteen to twenty years ago when as few as 15% of family physicians in North Carolina regularly delivered babies. This finding parallels recent national studies.^{1, 6, 12}

Despite national trends for physicians to engage in group practices, North Carolina family physicians still often establish solo practices. The fact that about one in five family physicians in the state located in a rural area may suggest that the family physician is best prepared to practice in this setting. The physicians tend to remain in their practice locations for a long time.

Finally, resident training programs need to be sensitive to the realities of the medical practice world.^{6, 14, 15} There is evidence that family physicians provide services in a number of settings including the office, hospital, and nursing home, treat a broad spectrum of medical conditions, and serve the entire patient population from infants to geriatrics. The clinical content of family practice, as represented in this study, compares quite closely with the definitions and goals of the specialty, in particular for residency-trained family physicians. Regional differences were found in the national study^{3, 6} and are validated in the present investigation. Resident education programs need to meet the requirements for particular regions, as well as train physicians to treat the entire general population for a broad spectrum of illnesses in both ambulatory and hospital settings. The impact of the new breed of family physician specialist is now beginning to affect health care delivery in North Carolina. Privileges on hospital medical staff clearly need to reflect these changes through credentials in areas of training and demonstrated competency.

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Table 5
Ten Most Frequent Diagnosis Clusters

Diagnosis Cluster	Rank	Frequency	Percent
General Medical Exam	1	1027	11.6
Acute URI	2	753	8.5
Hypertension	3	637	7.2
Diabetes Mellitus	4	425	4.8
Pre- and Postnatal Care	5	398	4.5
Soft Tissue Injuries	6	336	3.8
Acute LRI	7	319	3.6
Urinary Tract Infections	8	283	3.2
Depression Anxiety	9	266	3.0
Otitis Media	10	257	2.9
Total		4701	53.1

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Bulletin Board

Genetic Clinics

For the past year, the Division of Health Services has been providing Genetic services to the citizens of the North Central Region of North Carolina. These services have, in part, been provided through quarterly satellite genetics clinics and include medical genetic evaluations, testing, counseling and follow-up to at-risk families. Risk factors may include:

- patients with known familial (genetic) disorders.
- individuals with multiple malformations or birth defects.
- individuals with a birth defect and a positive family history.
- couples or families interested in genetic counseling regarding risks of occurrence or recurrence of familial disorders or birth defects.

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IN STATE

February 17-18

"Clinical Teaching"

Place: Chapel Hill

Fee: \$275.00

Credit: 12

Info: Ms. Ruth De Blik, ORDEHP, UNC School of Medicine, 322 MacNider Bldg., 202H, Chapel Hill 27514. 919/966-3641

February 19-22

"Beyond Advanced Clinical Teaching Skills"

Place: Rougemont

Credit: 20 hours Category 1 AMA

Info: Dr. Katharine Munning, 407 Crutchfield Street, Durham 27705. 919/471-2571

February 20-22

"Selected Topics for the Practicing Clinician"

Place: Durham

Credit: 24 hours Category 1 AMA

Info: Cindi Easterling, Box 3306, Duke University Medical Center, Durham 27710. 919/684-6485

February 24-26

"NCSIM/NC-ACP Joint Meeting"

Place: Greenville

Info: Kathy Adams, North Carolina Medical Society, Box 27167, Raleigh 27611. 919/833-3836

March 1-3

"2nd Annual Diving Accident Symposium"

Place: Durham

Credit: AMA, AAFP, ACEP

Info: Cindi Easterling, Box 3306, Duke University Medical Center, Durham 27710. 919/684-6485

—women with a history of 3 or more spontaneous abortions.

A calendar of clinics has been scheduled for 1984. The dates are as follows:

Tuesday, March 13, 1984

Tuesday, June 5, 1984

Tuesday, September 25, 1984

Clinics are held at the Developmental Evaluation Center, 2311 W. Cone Blvd., Suite 143, Greensboro, N.C. Approximately six new families can be scheduled at this time. Appointments may be made by calling the DEC at (919) 282-1100 or by contacting Ms. Beverly Tenenholz, at the Division of Health Services in Winston-Salem, N.C. (919) 761-2390.

March 6

"Duke Tuesday"

Place: Durham

Credit: 5 hours Category 1 AMA

Info: Linda Mace, Box 3707, Duke University Medical Center, Durham 27710. 919/684-2033

March 6-7

"The Least Restrictive Alternative: Programmatic and Management Issues"

Place: Raleigh

Info: 919/966-5463

March 7-10

"Internal Medicine: 1984"

Place: Chapel Hill

Credit: 25 hours Category 1 AMA

Fee: \$250.00

Info: William B. Wood, M.D., 231 MacNider Bldg 202H, UNC School of Medicine, Chapel Hill 27514. 919/962-2118

March 15-16

"Eighth Annual Cancer Research Symposium"

Place: Chapel Hill

Credit: 11 hours Category 1 AMA

Info: Mrs. Mimi Minkoff, Cancer Research Center, UNC School of Medicine, Chapel Hill 27514. 919/966-3036

March 18-21

"Improving Residency Rotations: Curriculum Planning and Negotiation"

Place: Rougemont

Credit: 20 hours Category 1 AMA

Info: Dr. Katharine Munning, 407 Crutchfield Street, Durham 27705. 919/471-2571

March 28-31

"Clinical Epidemiology"

Place: Chapel Hill

Credit: 24 hours

Info: Ruth De Blik, 322 MacNider Bldg. 202H, UNC School of Medicine, Chapel Hill 27514. 919/966-3641

April 7

"13th Annual New Bern Symposium: Infections Disease"

Place: New Bern

Info: William B. Hunt, Jr., M.D., Box 2157, New Bern. 919/633-8607

April 8-11

"Administrative Skills: Faculty as Managers"

Place: Rougemont

Credit: 20 Hours Category I AMA

Info: Dr. Katharine Munning, 407 Crutchfield Street, Durham 27705.
919/471-2571

April 10

"37th Annual Medical Symposium: Pulmonary Medicine"

Place: Greensboro

Info: L. S. Slotnick, M.D., 1018 North Elm Street, Greensboro 27401
919/275-7238

April 11-14

"3rd Annual Spring OB/GYN Symposium"

Place: Durham

Credit: AMA, ACOG

Info: Cindi Easterling, Box 3306, Duke University Medical Center,
Durham 27710. 919/684-6485

April 12

"North Carolina Neuro-ophthalmology Review"

Place: Chapel Hill

Credit: 2.5 hours Category I AMA

Info: Baird S. Grimson, M.D., UNC School of Medicine, Chapel Hill
27514.

April 20-21

"Carolina Ocultome Workshop"

Place: Chapel Hill

Credit: 13 hours Category I AMA

Info: David E. Eifrig, M.D., UNC School of Medicine, Chapel Hill
27514.

April 25

"Current Concepts in Otolaryngology for Primary-Care Physicians"

Place: Chapel Hill

Fee: \$50.00

Credit: 6 hours Category I AMA

April 27

"Biochemistry Symposium"

Place: Chapel Hill

Info: William B. Wood, M.D., 231 MacNider Bldg. 202H, UNC
School of Medicine, Chapel Hill 27514 919/962-2118

OUT OF STATE**February 12-17**

"Postgraduate Course in Diagnostic Imaging"

Place: Cancun, Mexico

Fee: \$475

Credit: 25 hours Category I AMA

Info: Donald R. Kirks, M.D., Box 3834, Duke University Medical
Center, Durham 27710. 919/681-2711, ext. 286 or 287

February 20-22

"Gold Coast Seminar: Surgery"

Place: West Palm Beach, FL

Credit: AMA, AAFP

Info: Continuing Medical Education, Box 3306, Duke University
Medical Center, Durham 27710. 919/684-6485

February 22-25

"Medical Computing"

Place: Key Biscayne, FL

Credit: AMA, AAFP

Info: Cindi Easterling, Box 3306, Duke University Medical Center,
Durham 27710. 919/684-6485

March 4-10

"Sports Medicine"

Place: Snowshoe, WVA

Credit: 20 hours Category I AMA

Info: Cindi Easterling, Box 3306, Duke University Medical Center,
Durham 27710. 919/684-6485

March 5-7

"Gold Coast Seminar: Pediatrics"

Place: West Palm Beach, FL

Credit: AMA, AAFP

Info: Continuing Medical Education, Box 3306, Duke University
Medical Center, Durham 27710. 919/684-6485

March 8-11

"New Horizons for Psychosomatic Medicine"

Place: Hilton Head, SC

Credit: 20 hours Category I AMA

Info: Joan K. Erpf. 316/379-0191

April 9-11

"Gold Coast Seminar: OB/GYN"

Place: West Palm Beach, FL

Credit: AMA, AAFP

Info: Continuing Medical Education, Box 3306, Duke University
Medical Center, Durham 27710. 919/684-6485

Letters to the Editor

Herpes Zoster Ophthalmicus

To the Editor:

There is an ever-threatening and rising incidence of Herpes Zoster Ophthalmicus (shingles arising from infection of the gasserian ganglion in the middle fossa of the skull). Because of the seriousness of this formidable disease with its complications leading to blindness and trigeminal neuralgia (corneal damage, irido-cyclitis, retino-choroiditis, and optic nerve involvement, leading to atrophy), prompt diagnosis is of the utmost importance. This is particularly true when erythema and papular formation is seen on the tip of the nose or alongside the nose, indicating that the naso-ciliary branch of the ophthalmic division of the trigeminal nerve is involved, which indicates the impending involvement of the ocular structures in 100% of the cases.

Prompt therapy, such as steroids, Decadron, must be given at once in large doses and then tapered off over the next 5-7 days. This therapy eliminates the entire pathologic process within 48 to 72 hours.

Analgesics are given to relieve the pain for the first 24 hours but no hospitalization is necessary. Patients may return to work within 24 to 48 hours.

Milton J. Friewald, M.D.
2401 Pennsylvania Avenue
Philadelphia, PA 19130

Thorotrast

To the Editor:

In the September 1983 issue of the *NC Medical Journal* Drs. Merlo, Faulk, and Dudley presented and discussed a case of Thorotrast-induced hepatic malignancy. They suggest that serial abdominal radiographs are useful in surveillance of thorium-exposed patients;¹ however, this is not substantiated by objective data.

We are following a patient referred for evaluation thirty years after injection of Thorotrast for cerebral arteriography. She has asymptomatic thorium deposits in her liver and spleen; liver-spleen scan, blood counts, and serum chemistries are all within normal limits. A literature search revealed very little objective data on early detection of Thorotrast-induced malignancies. Despite extensive follow-up data and well documented increases in both malignant and non-malignant morbidity and mortality by the Japanese² and other national Thorotrast studies, there are no prospective studies attempting to establish predictors of these complications.

There have been several studies observing the prevalence of x-ray, serum chemistry, blood cell, and chromosome abnormalities, but these results have not been correlated with eventual outcome. Only Janower and associates³ have prospectively examined exposed subjects with comparison to a control group. They found "apparent" differences in Bromsulphalein retention and alkaline phosphatase and a marked increase in the number of chromosome

aberrations. Unfortunately, they had only thirty-four subjects, followed them for only three to four years, and did not correlate their findings with outcome.

A major reason for the absence of prospective studies may be best expressed by Oliveira and colleagues in their description of the experience in Portugal: "People injected with Th⁹⁰ are aware they have a potential malignant condition (caused by medical treatment) and they avoid doctors and hospitals, refusing periodic clinical and laboratory examinations."⁴ Intensive follow-up has been further discouraged by the absence of good therapy for most of the complications described. Despite a recent report of early detection and subsequent successful resection of a Thorotrast-induced cholangiocarcinoma,⁵ there are no effective interventions for most of these patients.

Serial abdominal radiographs may be of use in follow-up of this group of patients; however, there is no literature support for this or other surveillance procedures. This is an excellent example of extensive epidemiologic data collection in identification and description of a problem; however, this has been of little aid to the practicing clinician in determining appropriate follow-up and surveillance of individuals at risk for these iatrogenic complications.

Bayard L. Powell, M.D.
Johnny B. Craig, M.D.
Bowman Gray School of Medicine
Winston-Salem, NC 27103

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Emergency Use of Epinephrine

To the Editor:

I would be very grateful if you could alert members of the North Carolina Medical Society to the following needs:

1. According to the North Carolina Board of Medical Examiners in excess of 1,500 non-physicians have been trained and licensed in accordance with 21 NCAC 321 this last year to administer epinephrine in the emergency situation of an adverse reaction to insect venom, drugs or foods. To be relicensed, these individuals must take a refresher training course annually.

2. There is a great need for physicians, especially allergists, to conduct these brief (½ hour) training courses to not only requalify those already in the program, but add to this pool trained non-physicians, who, like those trained in CPR, can administer life-saving aid when a physician is not immediately available.

3. I would be very glad to supply materials and any other

assistance to any physician wishing to devote a little time to this vital program. In addition, the State Office of Emergency Medical Services at the Department of Human Resources, PO Box 12200, Raleigh, NC, 27605-2200 can be contacted for regulations covering the program and for the necessary forms.

Claude A. Frazier, M.D.
Doctors Park
Asheville 28801

Problems with DRGs: A Letter to Dewey Dorsett, M.D., President of Metrolina Medical Peer Review Foundation, Inc.

Dear Dr. Dorsett:

I am writing to you on behalf of the medical staff of Lincoln County Hospital. At a recent meeting, the medical staff adopted the following resolution: "Be it resolved that the Professional Review Organization be requested to provide a PSRO staff physician consultant to be available by phone to provide consultation on admissions and with the power to authorize admission for those patients over whom they have hospital review authority when the attending physician is *in doubt* about PSRO approval."

This letter is being written to request that the Medical Peer Review Organization give serious consideration to the adoption of a physician consultant service in view of the continuing problems with review and approval of patient admission. The reasons for the practicality of such a physician consultant to act as a preadmission consultant and approval source follow.

1. A problem arises when an attending physician is in doubt about PSRO approval of an admission which the attending physician feels is needed. The attending physician needs to have the benefit of talking to a PSRO physician to obtain approval or disapproval.
2. It is assumed that the capacity of the PSRO to give retrospective review to admissions will increasingly work to disadvantage the attending physician (and of course the hospital and the patient) as the review is always made after the admission criteria have been satisfied by the attending physician, and as the review by a PSRO physician is always from a retrospective viewpoint. The provision of a preadmission consultation will provide that the consulting physician will always be involved at the level of the attending physician, which is from a prospective viewpoint.
3. It is felt that the implied and the explicit negative bias that increasingly enters the attending physician's decision-making to determine admission is brought about by the pressures of peer review and by PSRO's zeal to reduce admissions within their jurisdiction.
4. It is felt that increasingly the attending physician will and can make decisions that are detrimental to his or her own best judgment and to the patient's best care because of the overriding pressure of possible peer review disallowment of the admission.
5. There will undoubtedly develop in the near future cases in which problems will arise which are serious in that there can be a violation of someone's rights. They can give rise to malpractice cases and they can cause ir-

reparable damage to the doctor-patient relationship. We feel it is important that the consulting PSRO physician be involved in this particular facet of the physician-patient relationship, as the pressures are now toward preventing the allowance of judgment errors that actually would be taken from the standpoint of the safety of the patient's health (e.g., errors on the side of safety), and of the physician's moral or judgmental, as well as legal, responsibilities.

6. We are aware that there have been, and will continue to be, instances wherein strongly held positions by the attending physician are overridden. Admissions or stays that have been denied are those involving cases of fever of undetermined origin, stroke, angina, syncope, and acute jaundice with accompanying illness. These are a few of the known examples when disallowment has occurred. At this institution patients have been disallowed admission or sent home early on the basis of alleged overstay, and within a matter of hours or days the patient was worse or dead.
7. It is known that there are variations in opinions by the reviewing physicians about the application of the criteria and standards of care of each case. In view of these human judgment errors or variances, as well as the opinions that are forthcoming from such situations, the physicians at Lincoln County Hospital feel that it is very important that the reviewing physicians be made available to participate in the prospective care judgments that the attending physician faces rather than benefit only from the safer retrospective judgments of which all attending physicians could benefit, if they were allowed to work only from that position in the care of their ill patients.

The Lincoln County Hospital medical staff feels very strongly about this concept, and feels it is important that the PSRO institute a workable plan that will fulfill the needs as outlined above. We further feel if private industry can provide preadmission consultation and authorization that is dealt with by a registered nurse (with an MD as back-up), that certainly something as important as this should be made equally available through the PSRO setting.

John R. Gamble, M.D.
Lincoln County Hospital
Lincolnton 28092

Containing Medical Care Costs

To the Editor:

"Doctor, if you don't mind, just go ahead and put me in the hospital to do those tests. My insurance will pay for it that way. I have been paying that company for 20 years. Now I am going to get my money's worth."

I offer an answer to Dr. Phillip's question #3 in his editorial page 770 in the December issue of the *Journal*. He asks, "How does one stop some doctors and hospital administrators from excessively using beds . . . especially when there is a strong financial incentive involved?"

The hypothetical patient's question above illustrates one situation in which the physician is in a difficult position to hold down medical care costs. In this situation the physician has basically two choices: 1. The physician makes the

patient happy and pads his own retirement fund by admitting the patient. 2. The physician stands fast as the vanguard of medical care costs, refuses to admit the patient, saves the insurance company \$500.00, maintains his ethical standards, and loses \$100.00 and the patient, who goes to Dr. Jones to be admitted.

There are many situations in which the choices are similar: the illness which could be treated at home if the patient and family were willing, the diagnostic problem which could be approached with maneuvers in a stepwise fashion versus a shotgun battery of tests, the patient who wants the extra lab or x-ray "just to be sure. My insurance will pay anyway."

I would prefer to believe that our professional ethics dictate decisions appropriate for good medical care of our patients regardless of the financial benefit to us. Observation tells me otherwise. It is unrealistic to give doctors the checkbook of our medical care account, reward them for spending the money, and then expect to control medical costs.

The answer lies in the patient's attitude. If the patient says, "Doctor, can't we treat him at home?" or "I want to be discharged as soon as possible," the physician will have the appropriate incentive to cut costs, when it is appropriate. Given the patient's urge to cut costs I submit that most physicians will do so when appropriate and only when appropriate.

Of course the patient must have some incentive himself. That incentive, of course, must be his own pocketbook.

Medical costs have been so effectively hidden from our patients that they see no relationship between their own medical insurance premiums and their use of medical facilities. Similarly in the "nonprivate" arena Medicaid conveys the "right" to medical care at convenience without restraint.

Patients must see a cost to themselves for each encounter with the medical system to supply an edge of restraint. The cost need not be large, and in the realm of Medicaid certainly should not be large enough to preclude medical care for a severe problem. The cost to the patient will be communicated to the physician and will be translated into restraint by the physician as he spends the patient's money.

A side effect of returning to a system closer to "pay as you go" is promotion of a more realistic view of the world. Currently our credit cards, checkbooks, and vast array of apparently free government services hide the fact that we all pay for what we get (though we are all convinced that we pay respectively more than our share). A healthier system in my view is one in which everyone is forced to see the cost and benefit of his actions at the time of his actions. Restraint is then internal and individual — much less expen-

sive than an "agency" or "department" in charge of restraint — and less unsettling than the idea of an arm of government handing out or withholding medical care.

Cost containment incentive can be effectively directed at the physician. In prepaid medical care plans the physician is rewarded financially for frugality in the use of medical facilities. This is appropriate in my view only when the patient is similarly rewarded. An adversary relationship between doctor and patient is established when only the doctor has incentive to use the brakes. (Just such a system is in use in Blue Cross/Blue Shield's new "Personal Care Plan for the Piedmont.")

I am not sure how to accomplish a change in the direction I have described. Dialogue, certainly, is a start. I invite comments.

Evan A. Ballard, M.D.
Jonesville Family Medical Center
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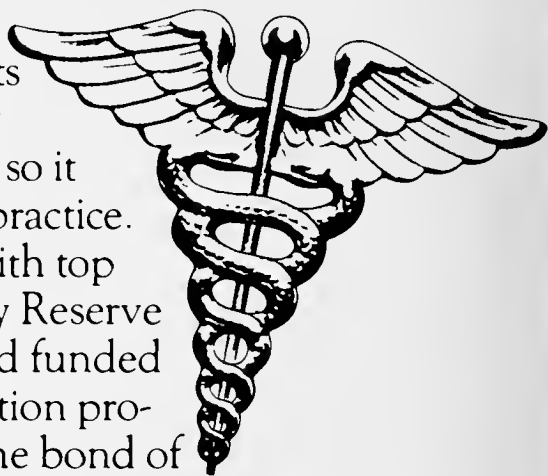
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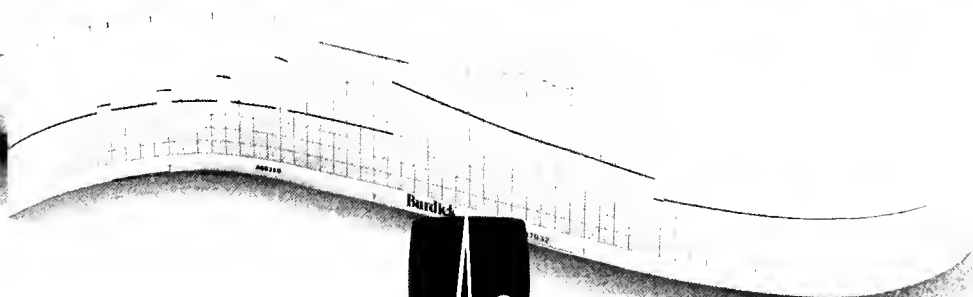
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March 1984, Volume 45, No. 3

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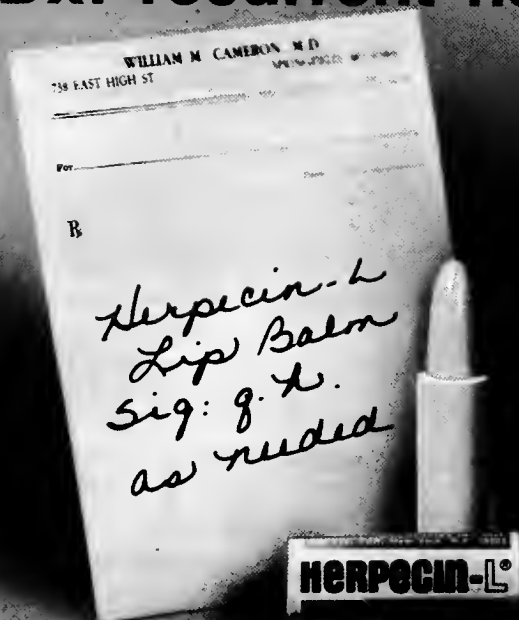
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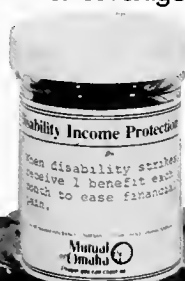
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HOUSE OF DELEGATES Meetings Scheduled

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Sessions of the HOUSE OF DELEGATES will convene in the Cardinal Ballroom, Pinehurst Hotel, Pinehurst, North Carolina, at the following times:

Thursday, May 3, 1984 — 10:00 a.m. — Opening Session
Saturday, May 5, 1984 — 2:00 p.m. — Second Session

A member of the CREDENTIALS COMMITTEE will be present at the Desk in the Hotel Lobby, Wednesday, May 2, 1984, 3:00 p.m. to 5 p.m., and Thursday, May 3, 1984, 8:30 a.m. to 10:00 a.m. to certify Delegates. Delegates are urged to bring their Credential Cards for presentation at the Registration Desk. Delegate Badges must be worn to be seated in the HOUSE OF DELEGATES.

REFERENCE COMMITTEE HEARINGS

Reference Committee hearings are scheduled to begin Thursday, May 3, 1984, at 2:00 p.m.

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References:

1. Stone PH, Turi ZG, Muller JE. Efficacy of nifedipine therapy for refractory angina pectoris. *Am Heart J* 104:672-681, September 1982
2. Antman E, Muller J, Goldberg S, et al. Nifedipine therapy for coronary artery spasm. Experience in 127 patients. *N Engl J Med* 302:1269-1273, June 5, 1980

BRIEF SUMMARY

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INDICATIONS AND USAGE 1. Vasospastic Angina PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation; 2) angina or coronary artery spasm provoked by ergonovine or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

2. Chronic Stable Angina (Classical Effort-Associated Angina) PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance but confirmation of sustained effectiveness and evaluation of long term safety in those patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS

Known hypersensitivity reaction to PROCARDIA
WARNINGS: Excessive Hypotension Although in most patients the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA-treated patients whose surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal. Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure. Rarely, patients usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with light aortic stenosis may be at greater risk for such an event.

PRECAUTIONS **General Hypotension** Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema. Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug Interactions. Beta-adrenergic blocking agents. (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates. PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antihypertensive effectiveness of this combination.

Digitalis. Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Carcinogenesis, mutagenesis, impairment of fertility. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose.

Pregnancy. Category C. Please see full prescribing information with reference to teratogenicity in rats, embryotoxicity in rats, mice and rabbits, and abnormalities in monkeys.

ADVERSE REACTIONS. The most common adverse effects include dizziness or light headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients; transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes do not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Additionally the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, diarrhea, constipation, inflammation, joint stiffness, shyness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, and sexual difficulties. Very rarely introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

Laboratory Tests: Rare, mild to moderate transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGPT and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of PROCARDIA therapy. The clinical significance of these abnormalities is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms. Cholestasis, possibly due to PROCARDIA therapy, has been reported twice in the extensive world literature.

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The Beneficial Effect of a Phenytoin Loading Dose on Seizure Recurrence in Patients With Acute Repetitive Seizures: A Preliminary Report

Peter Gal, Pharm.D., Jack D. McCue, M.D., Michael Tate, B.S. and James Price, B.S.

PHENYTOIN is generally believed to be effective for the treatment of status epilepticus.¹⁻³ Recent studies usually recommend that a loading dose of 15-18 mg/kg be given intravenously to maintain serum phenytoin concentrations above 10 mg/L for 24 hours.²⁻⁴ Physicians are reluctant to use doses of this magnitude (in excess of 1 g for a 70 kg person), however, despite the demonstrated safety of this dosage regimen if the infusion rate is kept below 50 mg/min.²⁻⁵ Some of their reluctance may come from the lack of proof that loading doses reduce the frequency of seizure recurrence; our study addresses this question.

Method

Charts of patients 18 years of age or older, admitted to the Moses H. Cone Memorial Hospital from January 1979 through September 1983 with a diagnosis of seizure disorder were retrospectively reviewed. All patients included in the study (1) had an admission diagnosis of status epilepticus or several sequential generalized tonic-clonic or partial seizures; (2) were hospitalized for at least 48 hours; and (3) received phenytoin in the Emergency Room.

Information obtained included demographic patient data, seizure etiology, other anticonvulsants, and phenytoin doses. The physician and nursing progress notes were reviewed for any mention of seizure recurrence within 48

hours of admission, a period of time arbitrarily selected as the time for similar serum phenytoin concentrations to be achieved both in patients receiving an initial loading dose and in those begun on maintenance doses only. A loading dose was defined as an initial intravenous dose of 15 mg/kg or greater.

Results

Of the 55 cases included in the study (table 1), 41.2% of those patients not given an initial phenytoin loading dose had seizure recurrence within 48 hours compared with only 9.5% of those who received initial phenytoin doses of 15 mg/kg or higher ($p < 0.06$). Of those patients with no previous phenytoin or subtherapeutic concentrations, 2/17 (12%) receiving a loading dose and 8/16 (50%) not receiving a loading dose had a seizure.

The etiologies for the seizures were comparable for the two groups of patients: they included alcohol-related (23), metabolic (4), brain damage (3), and unknown (25). The highest recurrence rate overall was among patients with alcohol-related seizures (26%). One patient had a hypotensive episode after receiving a loading dose.

Discussion

The findings from this retrospective study support the importance of initiating phenytoin therapy with a sizable loading dose (15 mg/kg or greater) in patients with status epilepticus or sequential seizures. While the need for adequate serum phenytoin concentrations is generally

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Table 1

Seizure recurrence in patients with various pre-seizure serum phenytoin concentrations who either received a phenytoin loading dose (>15 mg/kg) or did not receive a phenytoin loading dose.

	Loading Dose			No Loading Dose		
	#Pts.	#Seiz.	%Seiz.	#Pts.	#Seiz.	%Seiz.
No previous phenytoin	7	1	14	6	3	50
Subtherapeutic concentrations (<10 mg/ml)	10	1	10	10	5	50
Therapeutic concentrations	4	0	0	8	3	38
Toxic concentrations (>20 mg/ml)	0	0	0	6	1	17
Unknown	0	0	0	4	2	50
Total	21	2	9.5	34	14	41.2

accepted, the consequences of giving an insufficient initial bolus are not usually appreciated. Our results indicate that the risk of seizure recurrence considerably outweighs the potential risk of a large intravenous phenytoin dose. When appropriate precautions are taken, such as slowing the intravenous infusion rate to 10 to 25 mg/min in elderly patients, loading doses appear to be safe.

The most significant design limitation in this study is our reliance on seizure observation and documentation in the chart by nurses and physicians; we believe, however, that a clinical event as dramatic as a seizure is likely to be detected and recorded by most health care personnel. An expansion of the number of patients studied is needed, but the difference between the loaded and non-loaded groups is

so large that the significant influence of phenytoin loading doses on seizure recurrence is likely to be further validated in a larger study.

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Affective Sickness and Normal Behavior

Arthur Freedman, M.D.

THE effort to improve the well-being of patients who are troubled by affective* disorders was for many years the most perplexing aspect of my practice. The language of psychiatry did not impart an adequate understanding of the processes involved, and the multiplicity of syndromes and the failure to distinguish consistently between qualitative and quantitative differences caused the classification of psychiatric diseases to be of only limited assistance. Nor was the assumption that psychiatric maladies resulted from unfavorable environmental situations altogether acceptable since so many people appeared to live through exceptionally trying experiences without ever having gotten sick at all. This latter observation has been affirmed in a review of the literature on this subject wherein the authors could not establish any clear relationship between stressful life events and psychiatric disease.¹

The realization that patients could be interrogated without interference from psychiatric preconceptions was slow to materialize. It gradually became apparent, however, that the symptoms that constitute the core of almost all the nervous or psychiatric maladies seen in my practice are but few in number, that they are stereotyped and repetitious, and that they can readily be arranged into three discrete categories. These have been identified, in accordance with their central features, as morning fatigue, aberrations of mood and trust, and obsessive thinking and tension.

An astonishing number of people report, when they are asked, that they are more fatigued when they get up in the morning than they were when they went to bed the night before. Since this is before any energy has been expended, it is not unlike the after-effects of certain infections. Some people are tired all the time, some regain their vigor later in the day, and a few become fully productive by evening. If morning fatigue is their only complaint, they fall asleep without difficulty, but many of them awaken too early, and claim that this is why they are tired. On the other hand enough of them sleep through the night, with or without hypnotics, for loss of sleep not to be an adequate explanation for their fatigue. It is interesting that although loss of appetite is what is usually described, many of these patients are obese, possibly because they overeat in their search for energy. In the end, the feelings of fatigue and the desire to eat are determined not by magic but by the chemistry of the brain.

* The dictionary says that affect relates to feelings and emotions and not to thoughts. But when the word is adopted by psychiatry, it must necessarily include both thoughts and attitudes. The word functional is not acceptable because most persons forget that function is dependent on structure.

From 317 West Wendover Avenue, Greensboro 27408.

Mood and trust disturbances are altogether different. Mood disturbances include sadness, an urge to withdraw, a sense of futility which may extend to ideas of suicide, and in women a propensity for spontaneous crying. Loss of trust, which is often but not always a companion abnormality, refers to a loss of confidence in one's self or in others, coupled at times with ideas of reference, hallucinations, or a feeling of foreboding. Such annoyances intrude on patients' consciousness suddenly and without provocation in the same way that seizure activity does, persist for minutes or hours, and then, just as suddenly vanish, only to reappear after a longer or shorter interval in exactly the same form. Except for the few who say that they have no problems and therefore could not possibly have a nervous illness, virtually all patients ascribe their discomforts to unhappy events in their lives. Many claim, too, that they are able to throw off their discomforts at will; but careful inquiry always reveals that their spells begin and end spontaneously. In this sense the only people who appear to be adversely affected by environmental events are those who are susceptible as a manifestation of their affective maladies. Patients feel entirely "normal" between spells even when the interval between them is quite short. And after their well-being has been restored they no longer are troubled by their mood and trust difficulties, even though the situations which they claimed were responsible for them remain unchanged.

The third component of affective illness is obsessive thinking. This pertains to the insistent preoccupation of patients with events that take place in their lives, and with such reactions as discouragement (not depression), grief, shame, guilt, and so on, that accompany them. People who are obsessed with these problems are unable to fall asleep promptly, but this bears no relationship to the experience of fatigue the following morning. Tension, which commonly accompanies this symptom complex, is not only a subjective experience, but it may also be manifest objectively in such findings as hyperreflexia, sighing respirations, fluttering of closed eyelids, cold sweating of the extremities, anal spasm, and tenderness of the suboccipital, trapezius, and anal levator muscles, and of the costosternal articulations. The detection of these findings during an examination provides a clue to the presence of previously unsuspected affective illness.

Terms such as stress, depression, schizophrenia, anxiety, emotion, subconsciousness, and others of similar ambiguity have not been employed because their connotations are misleading, because there is no consensus as to their meaning, and because in some instances they imply only mystical notions.

Inasmuch as the symptoms that have been described are

subjective, they cannot meet the present-day scientific requirement for documentation. Yet if they are perceived as the clinical manifestations of malfunctioning neurochemical processes, they may be regarded as finite, and this is how they are thought of by patients. Patients seem unable to communicate their discomforts in a straightforward manner; instead they almost always recount them in terms of what they believe to be the responsible causes.

The likelihood that the preceding descriptions accurately delineate discrete patterns of affective illness seems to be supported by the specificity of the clinical response of patients to selected medications. Three classes of drugs are effective: tricyclic compounds, in relatively small doses, rapidly abolish morning fatigue; thioridazine suspension (the least hazardous of the phenothiazines) eradicates mood and trust disorders, although less rapidly than the tricyclics dissipate fatigue; and minor tranquilizers ameliorate obsessive thinking and tension. These appear to act by slowing down the patient's gyroscopic mental activity, although they tend to aggravate mood disturbances should these happen to be present concurrently.

The well-being of patients has been improved with this regime quickly, safely, durably, often completely, and at relatively low cost. Patients have become able to perform up to their natural capabilities, and are no longer troubled by the situations they previously believed had provoked their malaise. Even though the maladies are in some instances cyclic, patients have fared better when their medications have been continued after their recovery, since relapses are common if the drugs are withdrawn. Compassion, although appealing, is not therapeutic; nor do people with affective disabilities seem to possess the ability to cope successfully. And since medications are administered as specifics, instead of as adjuvants to other forms of therapy, the treatment is not that of persons but rather of their neurochemical processes. Detailed personal histories are not needed; and when people do appear to be troubled by adverse circumstances, it is presumed that they have a predisposition toward affective types of illness.

These abnormalities are functional in that they are performance defects of organs and tissues. As such they are sufficiently distinctive to be considered as a nosologic entity, perhaps called affective brain syndrome. Manic states have been omitted because they are rarely encountered, as have the discomforts that are thought by many physicians as well as lay people to respond to counseling or placebos. Women are far more frequently affected than men, their complaints sometimes appearing in association with such events as menses, delivery, and menopause, which involve their reproductive systems. Media reports suggest that adolescents are more troubled than adults, but adolescents do not often seek medical attention for their difficulties. In the light of these observations, though, the influence of changes in hormonal patterns may be a relevant consideration.²

Abnormalities of affect are common in both general and specialty practices, but they are not always recognized. They occur as the sole disabilities of patients and also concurrently with illnesses which are conventionally called organic. Patients with these ailments do not always fare well, however, because of the professional compulsion to rule out structural changes in organs other than the brain. When the tests are normal the patients may be told that their symptoms are imaginary.

It has been my observation that when patients recover from affective ailments their symptoms, which previously had consisted of some combination of fatigue, mood and/or trust abnormality, obsessive thinking and tension, become replaced by qualities which are their approximate opposites. Ideally these are energy, aspiration, confidence and composure, although people do not often attain such an exalted state in full measure. Nevertheless, qualities like these can be only manifestations of something akin to normal neurochemical activity and therefore are also endogenous. The degree and hierarchy with which these qualities are expressed, on the other hand, are what make each individual unique.

The inference from the foregoing is that other fundamental characteristics of the mind are similarly inherent. These include the components of cognition, the aptitudes, the awareness of abstract concepts, and the values that quantitate the expression of each person's attributes. Behaviorists hold that the primary determinants of people's conduct are in the cultural environment, but it seems instead that the environment contributes content to qualities that in essence are inherent. This point of view also accounts for the variations in beliefs and practices that are encountered in different regions. The statistical studies of social scientists confuse this subject because they emphasize the homogeneous aspects of attitudes and behavior, but such studies actually measure only the molding effect of community pressures. If it is correct that neurochemical activity is the significant factor in the determination of behavior, then identification of the qualities by which it becomes manifest is a suitable subject for systematic study.

If the disorders of affect are viewed as abnormalities of neurochemical systems, they can be described with precision and treated with specifically acting medications. Since the symptoms of these disorders are perceived as the manifestations of endogenous processes, their opposites, the attributes of normality, must likewise be endogenous. The qualities that determine people's everyday behavior are therefore also inherent, and their modification by the cultural environment must be considered to be a supplementary contribution.

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Hearing Screening in "High Risk" Infants

Henry R. Boer, M.D., M.P.H.

THE exact number of infants born with significant hearing problems is uncertain, but estimates range from 1:700-1,000 in the normal term newborn¹⁻³ to 1:50-60 in the prematurely born infant or the infant sick enough to be admitted to a Neonatal Intensive Care Unit (NICU).³⁻⁵ Hearing is essential for the normal development of language and speech, and impairment of hearing may influence psychological adjustment of the normal developing child. To enhance appropriate management and early rehabilitation of infants with deafness, the optimum time for identifying infants at risk is early in life.

Since 1982 all infants admitted to the Moses Cone Hospital NICU have been screened for hearing deficits before discharge. This report deals with a subgroup of those infants with a birth weight less than 1,500 grams.

Materials and Method

The study population includes premature infants admitted to our NICU from February 1, 1982 through July 31, 1983. Thirty-eight infants had birth weights of less than 1,000 grams: of these, 15 were tested, 3 were transferred to other institutions, and 20 died. Fifty-two infants were admitted with a birth weight between 1,000 and 1,500 grams. Forty-nine of these infants were tested, 2 were transferred and 1 died. Infants were tested using the Crib-O-Gram⁶ a few days before discharge from the hospital when they were assumed to have no medical problems. The apparatus consists of a motion-sensitive transducer attached to the undersurface of the infant's bassinet which detects movements of the infant in response to a sound stimulus presented at scheduled intervals. A score of 50 or above was considered a "pass." Infants who failed the test were retested on two subsequent occasions. Infants who failed all three tests were studied further with brain stem evoked potential.

Results and Discussion

In 1973 a joint committee on infant hearing screening, with representatives from the American Speech and Hearing Association, the American Academy of Pediatrics, and the American Academy of Ophthalmology and Otorhinolaryngology cited five factors most often associated with hearing impairment in infants.⁷ These factors were affected families; congenital rubella; defects of ear, nose and throat; bilirubin levels in excess of 20 mg/dl; and birth weight less than 1,500 grams. Studies by Feinmesser² and Simmons et al⁸ have shown that additional factors such as maternal bleeding, difficult delivery, a 5 minute Apgar score less than 6, neonatal respiratory distress, sepsis and bilirubin

level greater than 12 mg/dl also should be considered high risk factors. Of these, the most important are complicated deliveries and low Apgar scores.

Infants with similar birth weights were grouped and several factors commonly associated with hearing defects were analyzed.* In these weight categories, there were no babies with facial abnormalities, intrauterine infection, or a family history of deafness.

(1) Hypoxia. Hypoxia causes a loss of cochlear nuclei,⁹ and Kileny et al¹⁰ found statistically significant differences in auditory brain stem responses when they compared asphyxiated neonates with a group of healthy newborns who were matched for gestational age and weight. Anagnostakis et al¹¹ found that 8 of the 9 children with hearing damage in a group of 98 survivors of infants with a mean birth weight of 1,540 grams had suffered from apneic spells during the neonatal period. I looked at factors that might be associated with perinatal oxygen deprivation. Several babies had low 5 minute Apgar scores or required high percentages of oxygen and respiratory support; most of them weighed less than 1,000 grams. All babies weighing less than 1,000 grams, in fact, had repeated episodes of low pO₂ values on arterial blood gas analysis — potentially significant hypoxic insults. None, however, failed the Crib-O-Gram.

In our institution, we treat apnea vigorously with theophylline. Our protocol calls for the use of theophylline when the baby has three apneic spells that last longer than 20 seconds in any given 24 hour period. Serum theophylline levels are followed and theophylline treatment is discontinued gradually after an infant has been free of any apneic or periodic breathing spells for 3 days. Aggressive treatment with theophylline was probably responsible, I believe, for the absence of deafness in these high risk babies.

(2) Hyperbilirubinemia. In babies with neonatal hyperbilirubinemia, deposition of bile pigments may be found in the basal nuclei, including the cochlear nuclei.¹² All but two of our infants had bilirubin levels less than 12 mg/dl, and most of them had levels well below 10 mg/dl. In our institution, hyperbilirubinemia in prematurely born infants is treated with phototherapy at levels of 6 mg/dl, making severe hyperbilirubinemia uncommon. This is, I believe, responsible for the absence of deafness in our hyperbilirubinemic babies.

(3) Aminoglycosides. The role of aminoglycosides in the pathogenesis of hearing deficits is still not clear. Barr,¹⁴ in a review, found few cases of ototoxic effects of aminoglycosides even after prolonged therapy during pregnancy.

* Complete tables with weight categories and risk factors may be obtained from the author.

Other investigators found no evidence of ototoxicity in low birth weight infants.^{11, 15} Our small infants often had, as expected, repeated doses and prolonged courses of gentamicin treatment. None, however, failed the test.

(4) Low Birth Weight. Mencher et al,¹⁶ reviewing many factors that may influence hearing testing in newborns, concluded that the most effective remaining method for examining newborns' hearing is some form of observable change in behavioral activity associated with an auditory stimulus. None of the 64 babies with a birth weight less than 1,500 grams failed the Crib-O-Gram; two had to be tested three times, but passed with scores well above 50 on the third attempt.

Summary

There is no reason to believe that our babies are different from those commonly encountered in the neonatal units across the U.S.A. All were premature, many had perinatal complications, and several had low Apgar scores and repeated hypoxic insults. Our vigorous treatment of hyperbilirubinemia and extensive use of theophylline in the prevention and/or treatment of apnea, however, may be different from practices in other neonatal units. It may well be that this is, in large part, the reason I did not find hearing deficits in our study population.

All the premature infants are followed up in our High Risk Clinic where they receive developmental assessments at regular intervals. None of the infants was subsequently found to be deaf. It is too early, however, to know if they

have the same perception for subtleties of sound, e.g. music appreciation, as the term infant not exposed to these risk factors. Screening of high risk infants for deafness is important so hearing impairment and deafness can be treated promptly.

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Heparin-Induced Thrombosis

William B. Herring, M.D. and Palmer F. Shelburne, M.D.

THROMBOCYTOPENIA following treatment with heparin has been recognized for many years, but heparin-induced thrombosis is less well-known despite the many reports of its occurrence since 1958. Its potentially serious consequences make it imperative that it be watched for in all patients on sustained heparin treatment. We recently encountered this complication of heparin therapy in a patient whose clinical course follows.

A 60-year-old man sustained an abrasion of his right leg while climbing steps. Healing was slow but there were no local signs of infection. Three weeks later he developed fever, sweating, and shaking chills. Fever to 103°F persisted without response to penicillin or erythromycin. He then had chest pain on deep inspiration but no cough, and was admitted to another hospital.

Thorough investigation for the cause of fever failed to yield a secure diagnosis. The chest X-ray on admission was normal, but by the fourth hospital day he had developed S₃ and S₄ heart sounds, cardiomegaly, pulmonary vascular congestion, and bilateral pleural effusions. There was sinus tachycardia with rates up to 150/min and ECGs showed left bundle branch block. Creatine kinase and lactate dehydrogenase isoenzymes were non-diagnostic. There was no evidence of volume overload. With vigorous treatment for congestive heart failure he improved and by the twentieth hospital day the chest X-ray had returned to normal. He had been afebrile since the ninth hospital day. On the thirtieth hospital day a radionuclide study showed symmetrical reduction of left ventricular contractility with a low ejection fraction of 36%. Acute myocarditis, probably of viral origin, was suspected but throat and rectal swab cultures for coxsackie- and echoviruses were negative, and acute and convalescent phase serum antiviral antibody titers were non-diagnostic.

A lung scan on admission showed perfusion defects in the left mid- and lower lung fields. Since the admission chest X-ray was normal these findings were thought indicative of pulmonary embolism. The arterial PO₂ was 69 mm Hg on room air. Other laboratory studies were normal, including a platelet count of 428,000/ μ l, prothrombin time of 12.5/11.0 sec, and activated partial thromboplastin time of 25/26 sec. Streptokinase, 250,000 u initially, then 100,000 u/hr for 24 hours was given IV, and then a continuous infusion of heparin was started. On the 15th hospital day, after treatment with heparin for 12 days at an average daily dose of about 50,000 u and an average aPTT of 52.4 sec (control 26.8 sec), his right foot and leg became numb, pale, and cold to the mid-calf. The platelet count was 40,000/ μ l (figure 1). A right femoral embolectomy

was performed, yielding about 10 cm of organized gray thrombus and a small amount of fresh clot. Heparin therapy was stopped for about 8 hours and was resumed postoperatively at an initial rate of 800 u/hr (19,200 u/day). The platelet count rose gradually over the ensuing 4 days to 179,000/ μ l. The heparin infusion rate was gradually increased to 1800 u/hr (43,200 u/day) but the aPTT did not exceed 41.5 sec. On the 5th day after resumption of the heparin infusion the platelet count dropped to 74,000/ μ l (figure 1). The patient developed pain and signs of ischemia in the left foot and leg. Aorto-femoral angiography revealed multiple adherent thrombi in the aortic arch, the descending thoracic and supra-renal abdominal aorta, and the left common iliac artery. There were also filling defects in both common femoral, left superficial femoral, left anterior and posterior tibial, and right peroneal arteries (figure 2). Bilateral iliofemoral and infra-renal aortic thrombectomy was attempted but the Fogarty catheter would not traverse the iliac arteries. There was excellent inflow. Multiple passes with Fogarty catheters distally to the ankle level failed to yield thrombus.

Heparin was discontinued and anticoagulation was achieved with coumadin. The platelet count rose to 426,000/ μ l by the 5th postoperative day and the patient recovered without further complications.

Discussion

The temporal relationships among heparin therapy, thrombocytopenia, and signs of vascular obstruction constitute evidence that heparin given as treatment for pulmonary embolism caused this patient's thrombocytopenia and thrombosis, although confirmatory *ex vivo* studies were not done. The recurrence of thrombocytopenia and massive thrombi upon retreatment with heparin is virtually conclusive.

Thrombocytopenia commonly follows heparin administration by continuous or intermittent intravenous or by subcutaneous routes. There are at least two types.^{1, 2} One occurs within 2 to 4 days after heparin treatment is begun, is mild and transient, and may resolve even if heparin is continued. The other is delayed, with more severe thrombocytopenia beginning usually after 6-13 days of heparin treatment (mean 9.8 ± 3.7 days, median 10 days) and reaching a nadir at 7-14 days. Mean nadir platelet counts were 29,000/ μ l and were as low as 5,000/ μ l.³ Withdrawal of heparin is followed by return of the platelet count to normal within a median time of 4 days (mean 5.6 ± 5 days). Readministration of heparin causes a prompt recurrence of thrombocytopenia.

The incidence of heparin-induced thrombocytopenia has not been clearly determined. In prospective studies with

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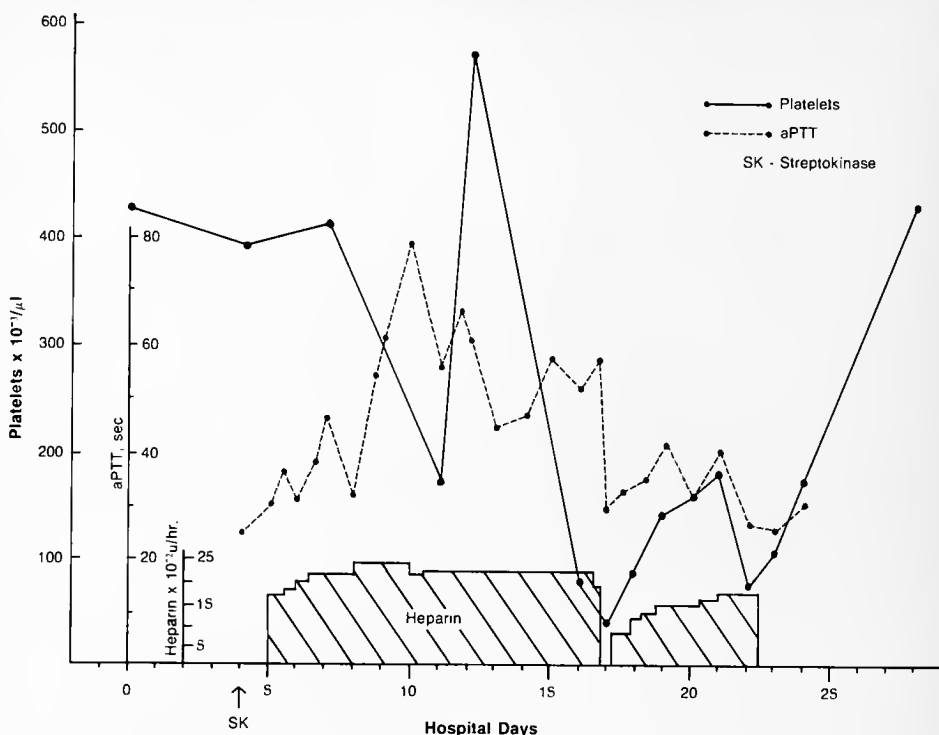


Figure 1. Relationships among platelet count, aPTT value, and heparin dose during the hospital stay of the patient.

monitoring by alternate-day platelet counts Bell and Royall, using bovine lung heparin, reported an incidence of 26% but only 7% when the heparin was of porcine gut origin,⁴ whereas Powers et al, using porcine gut heparin, found it to occur in only 3% of patients.⁵ The combined incidence from six prospective studies of patients treated with porcine gut heparin was 3.7%.² At the Moses H. Cone Memorial Hospital we have detected thrombocytopenia in one of 386 patients (0.3%) treated with beef lung heparin and in one of 256 (0.4%) treated with porcine gut heparin. Our true incidence may have been higher since our data were collected retrospectively and platelet counts were not routinely performed. Another factor contributing to a low incidence could be the generally short duration of treatment with heparin in our hospital (mean 6.0 ± 5.9 days, median 8 days).

Mechanisms

The mechanism of the early, transient form of thrombocytopenia is uncertain. Heparin may promote platelet aggregation by several mechanisms, including inhibition of platelet adenylate cyclase.² The consequent reduction of cyclic AMP releases the arachidonic acid pathway from inhibition, resulting in the release from platelets of thromboxane A_2 , a potent aggregant. Heparin also antagonizes the inhibitory effect of endothelial prostacyclin on platelet aggregation. Presumably platelet aggregation thus induced does not progress beyond the first phase, since it seems to

be reversible. Thrombocytopenia is due to transient sequestration of large numbers of platelets.¹ Our patient may have shown this phenomenon since his platelet count dropped from $413,000/\mu\text{l}$ on the second day of heparin treatment to $173,000/\mu\text{l}$ on the sixth day, followed by an abrupt rise before thrombocytopenia was noted on the eleventh day. Alternatively, the platelet count of $573,000/\mu\text{l}$ could have been erroneous (figure 1).

There is abundant evidence that the later-appearing, more severe form of thrombocytopenia is mediated by a heparin-dependent antibody to a component of platelet membrane.^{2, 3, 6, 7} The antibody is usually IgG but an IgM antibody has been described.⁷ The platelet-IgG-heparin interaction that causes aggregation may require complement.⁸ Aggregation of large numbers of platelets accounts for the thrombocytopenia. Platelet production is presumably uninhibited since bone marrow examination shows a normal or increased number of megakaryocytes.¹

Using a variety of methods for their detection, heparin-dependent antibodies could be demonstrated in only 72% of 71 patients with heparin-induced thrombocytopenia in 14 studies.² The most widely used technique is observation of platelet aggregation upon the addition of heparin to the patient's platelet-rich plasma, or to normal platelets suspended in the patient's serum, with appropriate controls. Since the antibody is predominantly platelet-bound, residual circulating antibody levels in thrombocytopenic patients would reasonably be low, although the concentra-

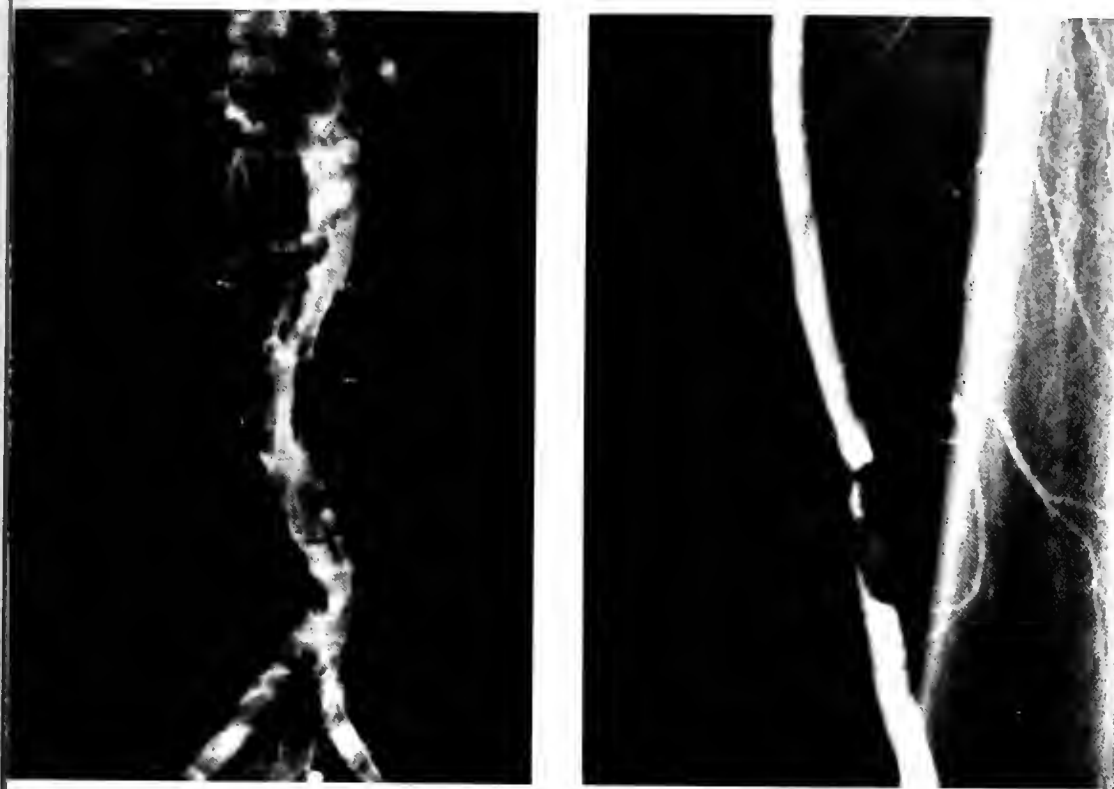


Figure 2. Angiograms showing filling defects in the abdominal aorta (left) and left popliteal artery (right).

tions of IgG and complement per platelet were found to be highest during thrombocytopenia.⁷ The removal of large amounts of antibody from the circulation by platelet aggregation, possibly of the most highly sensitized platelets, might account for the high frequency of negative tests.

Most evidence favors a lack of dependence of the reaction upon the dose of heparin or upon the route or mode of administration.² Cines et al, however, showed a relationship to dose in the amount of C₃ deposited on normal platelets by the plasma of two patients with heparin-induced thrombosis.⁸

The duration of the thrombocytopenic response to heparin is not well-established. Rhodes et al found it present up to 2 months after recovery from heparin-induced thrombocytopenia in two patients, but absent in a third at 4 months.⁷

Clinical Manifestations

Heparin-dependent antibody-mediated platelet aggregation of sufficient magnitude to cause thrombocytopenia is followed by clinical manifestations of vascular obstruction in a high proportion of cases. In 17 prospective studies reviewed by Carreras that totaled 73 patients there were 45 instances of thrombosis (62%). In vessels with high flow rates (arteries) the thrombi are composed predominantly of platelets and fibrin, with few leukocytes and rare red cells.

This has been called the "white clot syndrome."⁹ While most often causing arterial thrombosis, commonly of large vessels, heparin may also induce clotting in the venous circulation, sometimes with pulmonary embolism.^{3, 7} Other manifestations of heparin-induced thrombosis are myocardial infarction,⁷ vein graft occlusion,⁹ skin necrosis,¹⁰ stroke,³ and disseminated intravascular coagulation.¹¹ Surgical intervention is often required for thrombectomy or amputation.³ If recognition and cessation of heparin administration are timely, recovery usually follows, depending upon the nature of associated conditions,³ but outcomes may be fatal.^{7, 10, 12}

Thrombosis may occur without absolute thrombocytopenia, but the fall in platelet counts remains consistent with aggregation of large numbers of platelets.¹³ This emphasizes the importance of a baseline platelet count prior to starting heparin treatment.

Bleeding may occur from heparin-induced thrombocytopenia, with or without clinical evidence of thrombosis, but is less common than thrombosis. Carreras' review suggests an incidence of 22% (16 of 73). At least six patients who bled also had evidence of thrombosis.²

Thrombocytopenia occurring during heparin treatment is an indication for prompt withdrawal of heparin and anticoagulation, if necessary, with alternative drugs, usually coumadin. Aspirin and other antiplatelet agents have not been systematically evaluated for their ability to correct or

prevent heparin-induced thrombocytopenia or thrombosis, but aspirin has been shown to inhibit heparin-induced platelet aggregation in the platelet-rich plasma of a patient with a heparin-dependent antibody.² The effect of low-molecular-weight dextran⁹ is difficult to evaluate, since rapid recovery after withdrawal of heparin is the rule.

Heparin resistance has been noted in patients with heparin-induced thrombocytopenia.¹ It has been attributed to release of platelet factor 4, a heparin-neutralizing factor, from the stimulated platelets. It could also be due to depletion of antithrombin III consequent to heparin-induced coagulation, or to the thrombotic event for which heparin was administered, due to consumption of antithrombin III by irreversible binding to activated clotting factors. Since heparin accelerates this process, reduced antithrombin III levels may be seen in any patient given heparin, intermittently or continuously, for more than a few days. Antithrombin III deficiency may be acquired in a variety of other conditions by impaired synthesis (e.g., liver disease, diabetes) or by excessive loss (e.g., nephrotic syndrome). Drugs other than heparin (e.g., estrogens) may lower the antithrombin III activity of plasma. Antithrombin III deficiency may also be hereditary.¹⁴ Heparin resistance was present in our patient during re-administration of heparin, since with increasing doses to 1800 u/hr the aPTT failed to rise above 41.5 sec (figure 1).

Why, rather than remaining low, our patient's platelet count continued to rise for 4 days during the second period of continuous heparin infusion, albeit at lower doses (figure 1), is unclear. No drugs with known anti-aggregant properties were given during this period. Measurement of antibody and complement levels might have helped clarify this question.

When thrombocytopenia appears in a patient beyond the fourth day of heparin treatment, regardless of route of administration or dose, the presence of a heparin-dependent antiplatelet antibody should be suspected. Platelet aggregometry may confirm but not exclude the diagnosis. Thrombosis should be suspected if signs of vascular insufficiency are present. Doppler testing and/or angiography may be useful. Vague pain in the low back and thighs and abdominal pain and distention have been observed one or two days prior to clinically evident vascu-

lar obstruction. These symptoms may be of ischemic origin, due to small vessel occlusion, and a helpful warning of impending larger vessel thrombosis.²

Heparin-induced thrombosis should be preventable in most cases by monitoring of platelet counts and by awareness of the possible significance of vague pains and heparin resistance. We have modified our heparin treatment protocol to include routine platelet counts prior to administration of heparin and on alternate days after the fourth day of continuous treatment, and an antithrombin III level upon evidence of a requirement for increasing doses of heparin to maintain prolongation of the aPTT.

Acknowledgements

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Medical Education at the Moses H. Cone Memorial Hospital: A Brief History and Comment

William B. Herring, M.D.

THE Moses H. Cone Memorial Hospital is a legacy from the estate of Mrs. Bertha Lindau Cone, who died in 1947, given in memory of her husband, a co-founder of Cone Mills, now one of the world's largest manufacturers of textiles. From its opening in 1953 the Hospital has had a significant commitment to medical education. Between 1954 and 1967 rotating internships, up to 10 per year, were offered under the voluntary part-time supervision of members of the medical staff.

After a decade of vicissitudinous experience with the rotating internship, the medical staff and trustees of the Hospital concluded that affiliation with a medical school offered the best prospects for a successful program in medical education. The University of North Carolina School of Medicine was approached and, after the favorable outcome of a thorough feasibility study, an affiliation agreement was concluded in November 1966. The famous Millis Report¹ was published that same year and the Coggeshall Report² the year before; they advocated in-depth training for primary medical care in continuity with undergraduate medical education, i.e., abolition of the free-standing internship. This initial affiliation agreement embraced these recommendations, but gave equal weight to two other major aims; they were to provide a community hospital-based clinical experience for medical students who might as a result be attracted to a career in primary care practice, and to develop a structure for effective continuing education of the medical staff.

To implement the affiliation, one full-time hospital-based faculty member each in internal medicine and pediatrics was appointed by the departments of internal medicine and pediatrics of the School. As evidence of the School's commitment it was decided that these should be tenure-track appointments, fully salaried by the School. To insure the teaching services a voice in the conduct of medical staff affairs these faculty were seated on the Medical Board of the Hospital.

Immediately there began a steady flow of fourth-year medical students for acting internships in internal medicine and pediatrics. In the early years, substantial numbers of students from schools other than UNC came to Moses Cone for accredited clinical rotations but later, upon the expansion of class size, available positions became limited to UNC students. Eventually clinical clerkships in internal

medicine for third-year students and a few subspecialty rotations were offered and have been generally filled. Part of the second-year introduction to clinical medicine has been taught by full-time and clinical faculty for many years.

The Medical and Pediatric Teaching Services jointly developed a residency program in family medicine, which was among 16 programs that were approved at the first sitting of the Residency Review Committee for Family Practice on February 16, 1969. Our first residents were appointed in July 1969. This program flourished, but it soon became apparent that residencies in general internal medicine and pediatrics were needed, both to afford primary care training in these fields and to strengthen by interaction the family practice program. These were added in 1972 and steadily improved in quality as they grew in size. For about five years all three programs have been stable in size with most positions filled. Presently there are at each year-level of the three-year programs four positions in internal medicine, four in pediatrics, and six in family medicine, for a total of forty-two primary care residency positions.

In addition to the primary care residency programs there are or have been at various times a small number of residents at advanced levels rotating through obstetrics-gynecology, orthopedics, psychiatry, and some of the medical specialties. For many years there have been advanced trainees in anatomic and clinical pathology. This program was recently replaced by fellowships in dermal pathology and hematopathology.

Faculty growth has been commensurate with the increased numbers of students and residents. Since 1973 the full-time faculty has grown from one each in internal medicine and pediatrics to five in internal medicine, four in pediatrics, and three in family medicine. Nine are tenure-track; three are full-time or part-time clinical faculty. Also, the Hospital has hired two full-time hospital-based neonatologists for whom teaching is an integral function. There are part-time faculty in obstetrics-gynecology, psychiatry, and clinical psychology.

A large number of medical staff members, representing all specialties, make vitally important contributions to the teaching program and collectively comprise a large volunteer faculty. Their participation not only represents an essential augmentation of the faculty, for it is equivalent to several full-time positions, but also benefits students and

From the Moses H. Cone Memorial Hospital, Greensboro 27401-1020.

house staff by contact with highly skilled practitioners in all clinical disciplines. The contributions of the members of the Hospital's departments of pathology, radiology, and emergency medicine deserve special mention.

Residents entering the clinical training programs of the Moses Cone Hospital have come from 26 states and 41 medical schools. Since 1971 about 100 have completed their training and entered practice, two-thirds in North Carolina and the remainder in 20 other states. Although emphasis has been on preparation for primary care practice, about half those who have completed residencies in internal medicine have sought and secured fellowships in subspecialties of internal medicine.

The advent of the North Carolina Area Health Education Centers program in 1972 brought a new impetus and major changes in perspective to medical education at Moses Cone. The Hospital became an AHEC in 1974 and was charged with responsibility for health manpower development and continuing education compatible with the needs of a six-county area that includes Guilford, Rockingham, Caswell, Alamance, Randolph, and Montgomery counties. While the Greensboro AHEC has made important contributions in nursing, technology, and other medical support fields, the majority of its resources have been expended in graduate medical education at Moses Cone and in continuing education for practicing physicians in the area. Through the AHEC, the University of North Carolina is now the main source of funding for medical education at Moses Cone.

Initially, the teaching programs were handicapped by inadequate facilities. Office space had been converted from waiting areas, and conference rooms and visual aids were severely limited. Outpatient teaching had been conducted in the Guilford County Health Department building and organized around clinics operated by the Health Department. In January of 1970, when North Carolina began to participate in the Medicaid program, the Moses Cone Hospital medical staff accepted responsibility for operating those County-sponsored clinics deemed essential to the teaching programs. Medical staff physicians joined the small full-time faculty in providing services to County-sponsored patients and teaching of students and house staff.

Guilford County rendered valuable financial and staff support and has continued its contributions in exchange for services rendered patients who qualify for county sponsorship.

In 1978 the first phase of the Hospital's building and renovation program was completed, including an outpatient department and a spacious library with comprehensive resources. The educational components were funded by the University through the Greensboro AHEC, but for several reasons some compromises were necessary, requiring that space intended for patient care be modified and used temporarily for AHEC staff and faculty offices. The next phase of the Hospital's construction program is nearing completion and will provide, among other facilities, definitive educational space and a short-term rehabilitation unit, unique for our state. These new accommodations should enhance our continuing efforts to improve the quality and proficiency of educational services at Moses Cone Hospital.

The medical teaching programs of the Moses Cone Hospital have clearly met their initial aims. The North Carolina AHEC program has enjoyed considerable success in health manpower development, with significant contributions from the teaching programs of Moses Cone. As this goal nears fulfillment AHEC's alternative purpose, health manpower maintenance or continuing education, will become its main justification. The effective delivery of continuing medical education to physicians in small communities will not directly influence the availability of health services, but it is rural North Carolina's best insurance for quality medical care. AHEC now faces a fresh and even greater challenge. It will require new and ingenious strategies if "state of the art" medical care is to be made accessible to all our citizens.

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Community Hospital Training Programs: Underrated Options for Medical Education

Jack D. McCue, M.D.

A majority of hospitals that sponsor graduate medical education are non-tertiary care community hospitals with fewer than 400 beds,¹ yet a review of medical education literature reveals no descriptive studies of community hospital training. The Association of American Medical Colleges and the American Medical Association, accumulators of valuable statistics on medical education, can provide only quite limited information since data on community hospital programs are not kept separately. Faculty advisors who assist students in their choice of a residency program generally have a limited understanding of community hospital-based training programs because most of their professional activities have been limited to university centers. For good economic, political, and educational reasons, community hospital programs will continue to be important sites for graduate medical education; a broader understanding of their characteristics, strengths, and problems, like those cited below, is needed.

Benefits of Community Hospital Training Programs

1. **Education Flexibility.** Unlike most community hospitals, university hospitals have powerful vested interests, traditions, and requirements for primary care manpower; as a result, university hospital residents' schedules seem to be more shaped by an institution's traditions and the requirements of subspecialty accreditation than deliberate and personal planning for the individual residents' needs. The format of the internship year, for example, is essentially unchanged at university centers despite major changes in the personal and educational content of internship. Community hospitals can be flexible enough to personalize graduate medical education without the schedule disruptions that university programs would encounter. In addition, small programs can more easily provide sane on-call schedules, accessible role models who have worked out a balance in their career, community responsibilities and personal life, and give the emotional support needed to facilitate maturation and the achievement of the difficult personal tasks of early adulthood^{2,3} than is possible at large programs where faculty is often transient and less committed to medical education than to research. Ultimately, more personal and humane treatment of residents will, I believe, result in more humane treatment of their patients.

2. **Relevance to Medical Practice Needs.** Community hospital programs are better suited to meet some of the essential educational needs of today's residents, especially in the important curriculum of primary care medicine. Even

the future specialist who expects to spend his workday inserting small catheters into small coronary arteries soon discovers that most private practice specialists now must spend a substantial part of their time in primary care activities, a trend that will likely increase in the future. At most competitive university programs, the rarity of influential teachers who are experienced generalists (even within general internal medicine sections!) makes effective instruction in topics like common illnesses, practice management, or psychosocial issues commonly unavailable or deficient.⁴

3. **Clinical Resources.** Patients with undiagnosed and untreated problems are more likely to be encountered by community hospital residents. University hospital patients are typically evaluated thoroughly before admission, and most "fascinomas" never reach university centers now. Residents at community hospitals diagnose and treat tuberculous meningitis and brucellosis; severely burned patients with invasive pseudomonas cellulitis and refractory leukemias are more likely to be referred to university hospitals. Many common diseases are totally missed at a university hospital — a medical resident may, for example, never treat a typical case of infectious mononucleosis.

4. **Continuing Medical Education.** A major beneficial spinoff of community hospital training programs is increased communication between the university and practitioners through community-based educational programs. Because community-hospital-based faculty have a greater knowledge of the needs of practitioners, they can facilitate the design of continuing medical education that will actually influence patient care. Individual patient consultations for practitioners by the faculty are opportunities to teach by example the current opinions of what constitutes optimal medical care. Academicians also have much to learn from working with practitioners who are wise in the practical realities of private practice and properly skeptical of academic fads. Well-organized educational networks like North Carolina's AHEC⁵ and Washington's WAMI⁶ are examples of successful attempts to bridge the widening gaps in medical knowledge between the university and the practitioners through community hospital training programs.

Problems and Misconceptions

1. **Fear of Competition.** Community attitudes toward training programs are not uniformly supportive. Private practitioners and medical societies now often view community-based medical education as potential competition for patients and as a source of new physicians in communi-

From Moses H. Cone Memorial Hospital, Greensboro 27401-1020.

ties already experiencing a surplus — fears that are more pervasive than those outside private practice commonly realize.⁷ In addition, patients in non-metropolitan areas are often less sophisticated about medical education than those who use university hospitals — they may still believe that students and residents are untrained, inexperienced, and unsupervised. Community hospitals, necessarily very sensitive to local public opinion, are wary of such misconceptions, and fear the occasional mishap by a student or resident that brings adverse publicity.

2. A Doubtful Solution to Excessive Specialization. It is unclear whether, as hoped, residents from community training programs are less likely to subspecialize. The reports that more medical residents decide to practice general internal medicine when off-campus experiences are included as part of their training^{6, 8} could reflect just a national movement of graduate physicians into family medicine and general internal medicine, or perhaps the general influence of primary care training programs.⁹ It is probable that, overall, personal factors play a larger role than specific educational experiences in the decision to specialize.^{10, 11} Community hospital programs should, therefore, be supported for their own strengths, not because of their potential for correcting physician maldistribution or discouraging excessive subspecialization.

3. Ambiguous Faculty Academic Status. Faculty at community hospitals must struggle for recognition by the basic science oriented university faculty. Like divisions of general internal medicine and departments of family practice, community hospital faculty often fit uncomfortably into the current academic reward, retention, and promotion system. Publications, grant-catching ability, and national exposure, not the quiet scholarship, hospital service, and teaching efforts of community hospital faculty, are key to academic promotions and salary raises. While university department chairmen and deans seem now to be trying to recognize the special skills of off-campus medical educators, the system is still strongly slanted to retaining and rewarding faculty involved in basic science and high technology clinical research.

4. Not Cheap Medical Education. Unfortunately, community hospital training programs may well be more expensive than centrally-based university programs. Because there are fewer junior faculty members, fellows, and chief residents, and less subsidization of educational expenses by grants, foundations, and government funding, educational

costs must be largely paid from patient-care revenues. One might even argue that resident training at university medical centers is a relatively inexpensive by-product of research and tertiary patient care. Excellent teaching requires a fusion of cultivated and practiced communication skills and a secure belief in one's teaching abilities that is not often found in unpaid clinical faculty. Outstanding clinicians, regardless of their expertise in patient care, are rarely an effective substitute for full-time teaching faculty who earn only part of their income in clinical activities.

Conclusions

The advisors and mentors of medical students need to know that community hospital residency training programs differ in many positive ways from their university counterparts, and can provide humane medical education that is responsive to individual residents' personal needs. Many expectations, however, that such education uniformly has broad community and university support, is less expensive, leads to fewer subspecialists, and can easily draw on inexpensive and expert skills of voluntary faculty are probably largely incorrect. Ultimately, the single most important role for academic community hospital programs will be to bridge the widening knowledge gaps between the university and the practitioner.

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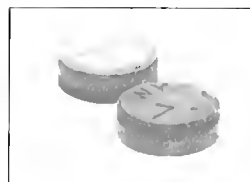
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CONTRAINDICATIONS

ASPIRIN: Allergic or idiosyncratic reactions to aspirin or related compounds.

MEPROBAMATE: Acute intermittent porphyria, allergic or idiosyncratic reactions to meprobamate or related compounds, e.g. carisoprodol, meprobamate, or carbamadol.

WARNINGS

ASPIRIN: Use salicylates with extreme caution in patients with peptic ulcer, asthma, coagulation abnormalities, hypoprothrombemia, vitamin K deficiency, or those on anticoagulants. In rare instances, aspirin in persons allergic to salicylates may result in life-threatening allergic episodes.

MEPROBAMATE: DRUG DEPENDENCE

Physical and psychological dependence, and abuse have occurred. Chronic intoxication from prolonged ingestion of usually greater than recommended doses is manifested by ataxia, slurred speech and vertigo. Therefore, carefully supervise dose and amounts prescribed and avoid prolonged use, especially in alcoholics and others with known propensity for taking excessive quantities of drugs. Sudden withdrawal after prolonged and excessive use may precipitate recurrence of preexisting symptoms, e.g. anxiety, anorexia or insomnia, or withdrawal reactions, e.g. vomiting, ataxia, tremors, muscle twitching, confusional states, hallucinations, and rarely convulsive seizures. Such seizures are more likely in persons with CNS damage or preexistent or latent convulsive disorders. Onset of withdrawal symptoms occurs usually within 12 to 48 hours after discontinuation; symptoms usually cease within next 12 to 48 hour period. When excessive dosage has continued for weeks or months, reduce dosage gradually over 1 to 2 weeks rather than stop abruptly. Alternatively, a short acting barbiturate may be substituted then gradually withdrawn.

POTENTIALLY HAZARDOUS TASKS: Warn patients meprobamate may impair mental or physical abilities required for potentially hazardous tasks, e.g. driving or operating machinery.

ADDITIVE EFFECTS: Since CNS-suppressant effects of meprobamate and alcohol or meprobamate and other psychotropic drugs may be additive, exercise caution with patients taking more than one of these agents simultaneously.

USE IN PREGNANCY AND LACTATION: An increased risk of congenital malformations associated with minor tranquilizers (meprobamate, chlorazepate, and diazepam) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. The possibility that a woman of child-bearing potential may be pregnant at time of institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physicians about desirability of discontinuing the drug.

Meprobamate passes the placental barrier. It is present both in umbilical-cord blood at or near maternal plasma levels and in breast milk of lactating mothers at concentrations two to four times that of maternal plasma. When use of meprobamate is contemplated in breastfeeding patients, consider the drug's higher concentrations in

breast milk as compared to maternal plasma levels.

USAGE IN CHILDREN: Keep preparations with aspirin out of reach of children. Equagesic[®] (meprobamate with aspirin) is not recommended for patients 12 years of age and under.

PRECAUTIONS

ASPIRIN: Salicylates antagonize uterine activity of probenecid and sulfinpyrazone. Salicylates are reported to enhance hypoglycemic effect of sulfonylurea antidiabetics.

MEPROBAMATE: Use lowest effective dose, particularly in elderly and/or debilitated, to preclude over-sedation. Meprobamate is metabolized in the liver and excreted by the kidney. To avoid excess accumulation exercise caution in its use in patients with compromised liver or kidney function. Meprobamate occasionally may precipitate seizures in epileptic patients. It should be prescribed cautiously and in small quantities to patients with suicidal tendencies.

ADVERSE REACTIONS

ASPIRIN: May cause epigastric discomfort, nausea, and vomiting. Hypersensitivity reactions, including urticaria, angioneurotic edema, purpura, asthma, and anaphylaxis may rarely occur. Patients receiving large doses of salicylates may develop tinnitus.

MEPROBAMATE: CNS: Drowsiness, ataxia, dizziness, slurred speech, headache, vertigo, weakness, paresthesias, impairment of visual accommodation, euphoria, oversatiation, paradoxical excitement, fast EEG activity. GI: Nausea, vomiting, diarrhea.

CARDIOVASCULAR: Palpitation, tachycardia, various forms of arrhythmia, transient ECG changes, syncope, hypotensive crisis.

ALLERGIC OR IDIOSYNCRATIC: Milder reactions are characterized by itchy, urticarial, or erythematous maculopapular rash, generalized or confined to the groin. Other reactions include leukopenia, acute nonthrombocytopenic purpura, petechiae, ecchymoses, eosinophilia, peripheral edema, adenopathy, liver, and drug eruption with cross-reaction to carbamadol, and cross sensitivity between meprobamate, meprobamate, and meprobamate.

carbamadol. Rare, more severe hypersensitivity reactions include hyperpyrexia, chills, angioneurotic edema, bronchospasm, oliguria, and anuria. Also, anaphylaxis, exfoliative dermatitis, stomatitis, and proctitis. Stevens-Johnson syndrome and bullous dermatitis have occurred.

HEMATOLOGIC (SEE ALSO "ALLERGIC OR IDIOSYNCRATIC") Agranulocytosis, aplastic anemia have been reported, although no causal relationship has been established, and thrombocytopenic purpura.

OTHER: Exacerbation of porphyria symptoms.

DOSEAGE AND ADMINISTRATION

Usual dose is one or two tablets, 3 to 4 times daily as needed for relief of pain when tension or anxiety is present. Not recommended for patients 12 years of age and under.

OVERDOSEAGE

Treatment is essentially symptomatic and supportive. Any drug remaining in the stomach should be removed. Induction of vomiting or gastric lavage may be indicated. Activated charcoal may reduce absorption of both aspirin and meprobamate. Aspirin overdose produces usual symptoms and signs of salicylate intoxication. Observation and treatment should include management of hyperthermia, specific parenteral electrolyte therapy for ketoadosis and dehydration, watching for evidence of hemorrhagic manifestations due to hypoprothrombinemia which, if it occurs, usually requires whole blood transfusions. Suicidal attempts with meprobamate have resulted in drowsiness, lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse. Some suicidal attempts have been fatal. The following data, reported in the literature and from other sources, are not expected to correlate with each case (considering factors such as individual susceptibility and length of time from ingestion to treatment, but represent usual ranges reported). Acute simple overdose (meprobamate alone). Death has been reported with ingestion of as little as 12 grams meprobamate and survival with as much as 40 grams.

BLOOD LEVELS: 0.5-2.0 mg percent represents usual blood level range of meprobamate after therapeutic

dosages. The level may occasionally be as high as 3.0 mg percent.

3-10 mg percent usually corresponds to findings of mild-to-moderate symptoms of overdose, such as stupor or light coma.

10-20 mg percent usually corresponds to deeper coma, requiring more intensive treatment. Some fatalities occur.

At levels greater than 20 mg percent, more fatalities than survival can be expected.

Acute combined overdose (meprobamate with other psychotropic drugs or alcohol). Since effects can be additive, history of ingestion of a low dose of meprobamate plus any of these compounds (or of a relatively low blood or tissue level) cannot be used as a prognostic indicator.

In cases of excessive doses, sleep ensues rapidly and blood pressure, pulse, and respiratory rates are reduced to basal levels. Any drug remaining in stomach should be removed and symptomatic treatment given. Should respiration or blood pressure become compromised, respiratory assistance, CNS stimulants, and pressor agents should be administered cautiously as indicated. Gureux, osmotic (mannitol) diuresis, peritoneal dialysis, and hemodialysis have been used successfully in removing both aspirin and meprobamate. Alkalinization of the urine increases excretion of salicylates. Careful monitoring of urinary output is necessary, and caution should be taken to avoid overhydration. Relapse and death, after initial recovery, have been attributed to incomplete gastric emptying and delayed absorption.

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One Community's Approach to Diabetes Education

Susan G. Drainville, R.N., B.S. and Robert E. Sevier, M.D.

RESPONSIBILITY for one's own care, a critical component in the treatment of chronic diseases, favorably influences prognosis and reduces acute hospitalizations. Indeed, self-management of chronic disease (with its prerequisite patient education) will likely be the rule, not the exception, as health care dollars and cost consciousness become the concern of both care provider and patient. In its search for quality education for those with one such chronic disease, diabetes mellitus, our community initiated a cooperative program to bridge the gap between hospital and community care. This collaborative program reduced duplication of services, pooled resources and provided patient services at less expense than could individual institutions or practitioners.

Community Diabetes Service (CDS) is an outpatient diabetes education and resource agency sponsored jointly by The Moses H. Cone Memorial Hospital, Wesley Long Community Hospital and the Guilford County Health Department in Greensboro, North Carolina. It serves the city of Greensboro and Guilford County, a metropolitan area in the Piedmont region of the state with an estimated population base of 320,000. CDS was founded in July 1981 with the following goals: 1) to provide direct teaching to patients and their families; 2) to provide in-service education and consultation to all members of the health care team; 3) to stimulate awareness of and community interest in diabetes; and 4) to meet the particular needs of the sponsoring institutions.

Background

There has been a long-standing recognition of the need for diabetes education in Greensboro. In the decade prior to the creation of CDS, some of these services had been provided on a part-time basis, initially by a unit of the United Way and later by a private home health agency. In February 1981, when such funding was no longer available, it became apparent that if a quality community diabetes education program were to continue, another sponsor needed to be found.

The Moses H. Cone Memorial Hospital was approached by several concerned physicians and citizens regarding support for a community diabetes education program. The hospital expressed interest in such a program but felt that it should be sponsored by more than one institution. Through the administrative support and personal efforts of the

Moses H. Cone Memorial Hospital's Chief Executive Officer, a preliminary program proposal was drafted to include program objectives, functions, services, accountability and a tentative budget.

To draft the proposal, data on patients with diabetes in the Greensboro/Guilford County area were collected by a diabetes nurse educator from the city's four hospitals and the county health department for the period October 1980 through April 1981. The data revealed that, for the six-month study period, 1,269 patients with diabetes had been seen and treated in these facilities but only 174 had received follow-up education.

Establishment of CDS

At several meetings during May and June 1981, the program proposal and supporting data were presented to representatives of the four Greensboro hospitals and the health department. After due consideration, two of the four hospitals, The Moses H. Cone Memorial and Wesley Long Community Hospitals, and the Guilford County Health Department elected to participate in and to give financial support to a community diabetes education program. The proposed budget is depicted in table 1; approximately 12% of the necessary revenues were to be generated through the agency itself with approximately 38% each contributed by The Moses H. Cone Memorial Hospital and Wesley Long Community Hospital, and the remaining 12% by the Guilford County Health Department.

TABLE 1
Budget for Community Diabetes Service

Salaries/Fringe Benefits		
Coordinator 25 hrs/wk	\$11,775.00	
Clerk-typist 10 hrs/wk	2,000.00	
SUBTOTAL	13,775.00	
Conference/Travel	500.00	
Subscriptions/Supplies/		
Education Materials	525.00	
Postage/Telephone	500.00	
Purchase of Literature for Sale	500.00	
Miscellaneous	200.00	
TOTAL EXPENSES		\$16,000.00
Revenue from Sale of Literature	500.00	
Revenue from Private Consultations		
Charged at \$10.00 per Visit and		
Anticipated Donations	1,500.00	
TOTAL REVENUE		2,000.00
BALANCE TO BE FUNDED BY SPONSORING ORGANIZATIONS		\$14,000.00

From Community Diabetes Service, 1200 North Elm Street, Greensboro 27401.

Community Diabetes Service could thus begin operation in July 1981, following a organizational period of only three months. The Moses H. Cone Memorial Hospital provided leadership and enthusiastic support in spearheading much of the detail work required for program implementation and donated office space. Elaine Button, R.N., an experienced diabetes nurse educator, was hired as the initial Coordinator for CDS and remains in that capacity to the present. Recognized as an effective patient educator, Mrs. Button had held comparable positions with the United Way and a private agency that had provided similar services within the community.

The Coordinator of the CDS program operates under the supervision of an advisory board comprising representatives from each of the sponsoring institutions, a local physician, and a representative from the Greater Greensboro Chapter of the American Diabetes Association. She meets quarterly with the Board to present a report of agency activities, including statistics pertaining to clients seen and services provided. She also prepares an annual report which is circulated to the Board and to the Chief Executive Officers of the sponsoring institutions. Working with the Advisory Board, she has prepared policies and educational objectives for the CDS program and, drawing from her personal experience in diabetes education and that of similar programs throughout the country, has developed a curriculum for the community classes that are offered by CDS.

A community program like CDS is highly dependent upon support from local physicians who appreciate the value of quality patient education. When the CDS program began, the Coordinator visited physicians' offices to describe the agency and its role in the community and made presentations at medical staff meetings. In addition, flyers are distributed monthly to physicians and house staff, institutions, local industries, and the public libraries to remind them of the on-going diabetes classes.

CDS Services

Table 2 lists the services CDS offers. The community classes are presented free of charge as four two-hour sessions each month and are offered both during the day and in the evening, primarily at public libraries throughout Greensboro. The four sessions cover the many aspects of diabetes management for patients and their families who are either self-referred or referred by physicians or in-hospital patient educators. Individual consultations usually require a physician referral with specific prescription as to which aspects of diabetes management are to be covered (e.g., dietary instruction, insulin administration, blood glucose monitoring, foot care). Following an individual consultation, the referring physician receives a copy of the education plan utilized and the Coordinator's assessment of the apparent effectiveness of the effort. While no patient is refused services due to inability to pay, a modest fee is requested. In 1981 this fee was initially set at ten dollars for a consultative session which usually lasts about forty-five minutes; at present it is fifteen dollars for the initial consultation and twelve dollars for subsequent visits. These charges have allowed modest budget increases from time to time without the necessity for increased contributions by the sponsoring institutions. While Community Diabetes

TABLE 2
Description of CDS Program

Outpatient:

1. Weekly classes (four-part series)
2. Individual consultations
3. Coordination of home care needs with patient, physician, other community resources
4. Home visits in unusual circumstances

Inpatient:

1. Discharge planning with hospital patient educators
2. Patient care conferences

Professional Education:

1. Education programs and resource materials to assist hospital staff to develop and refine nursing care of the patient with diabetes
2. Resource agency to nursing personnel and medical residents
3. Stimulation of research and study in diabetes among those interested in diabetes

Public Education:

1. Education programs planned to meet the needs of the community
2. Liaison with community agencies concerned with care of persons with diabetes
3. Lectures about diabetes for civic lay groups

Service is primarily a patient education and consultative service, the Coordinator also plans diabetes educational workshops to update and refine diabetes management knowledge and skills for both health professionals and patients.

The Results

The success of the CDS program is reflected in table 3. During its first two years of operation, CDS has served 875 clients, either in classes or in individual sessions. The sponsoring institutions have continued their enthusiastic support of the agency, recognizing the value of their investment in quality education. For the physician who has limited contact with diabetic patients and inadequate office personnel and resources for effective teaching, CDS provides invaluable and inexpensive access to a highly skilled and motivated diabetes educator. It thus offers a way to avoid duplication of personnel and reduce overhead costs by providing a community resource to any practitioner with diabetic patients. As table 3 implies, there is a gratifying utilization and support of CDS by a broad base of community physicians. Patient acceptance and response also has been excellent, as reflected both in questionnaires and in improved performance demonstrated by appropriate pre-

TABLE 3
CDS Statistics 1981-1982

Total Clients Seen	1981-1982	1982-1983	Total
Classes	301	307	
Consultations	93 (149 visits)	96 (163 visits)	
Discharge planning	27	44	
Home visits	7	0	
	428	447	875
Number of referring physicians	53	62	115

and post-testing. It is difficult to document reduced health care expenditures through avoidance of acute hospitalizations and reduced physician visits with CDS services, but we and participating physicians believe that initial hospitalization for education and instruction in self-management (e.g., insulin administration and regulation) has been avoided in a number of cases, and that the availability of intensive consultation through CDS has avoided re-hospitalizations.

In summary, the Community Diabetes Service program has efficiently and effectively met a growing community need in Greensboro/Guilford County since its inception in 1981. While such a collaborative effort is obviously not the only way to meet such a need, it is felt that CDS constitutes a model that may well prove useful to health care planners in other communities throughout the state as they seek to avoid duplication of services and to contain costs without compromising the quality of patient service.

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Features for Patients

Understanding Hypertension

Martin Johnson, M.D. and Angela Staab, R.N.

Approximately 20 million Americans have undiagnosed or inadequately treated hypertension (high blood pressure). It is known as the "silent killer" because the majority of hypertensive people feel perfectly well. On both a national and an individual level, the first step toward correcting this health problem involves public education — we hope the following discussion will facilitate a better understanding of hypertension.

How is the blood pressure measured?

Our blood pressure is created by (1) the forceful pumping of blood into the arteries by the heart and (2) the tension in the walls of the arteries (similarly, the water pressure in our homes is created by the force of the pump and the size of the pipes the water is pushed through). It can be measured directly by surgically inserting a small pressure monitor into an artery, or indirectly (the usual way) with a sphygmomanometer (blood pressure cuff) and stethoscope. The sphygmomanometer consists of an inflatable rubber bladder inside an arm (or leg) cuff, an inflating bulb, and a pressure gauge (manometer) from which the applied pressure is read. An accurate estimate of the blood pressure can be determined if the sphygmomanometer is properly calibrated and the proper sized blood pressure cuff is used. A cuff that is too small for the arm will give a falsely

high blood pressure reading and a cuff that is too large will give a falsely low blood pressure reading. The most accurate kind of pressure gauge is usually the mercury-type pressure gauge, because it rarely needs recalibration; the dial-type pressure gauges can wear out eventually, and they require periodic recalibration.

To measure the blood pressure, the proper sized cuff is secured snugly around the arm, which should be held at heart level. Enough air is pumped into the cuff to raise the bladder pressure high enough to actually (transiently) stop the blood flow through the arteries to the arm. Then, while listening with the stethoscope over an artery at the level of the elbow, the arm cuff is slowly deflated.

The indirectly measured systolic pressure corresponds to the pressure reading (in millimeters of mercury) at which turbulence, in the form of an initial tapping sound, is heard through the stethoscope. This is similar to standing on a garden hose and slowly releasing your weight; when water begins flowing through the hose, turbulence (which could be "heard" with a stethoscope if your neighbors aren't watching) occurs. The diastolic pressure corresponds to the pressure reading at which the tapping sound (and therefore, significant turbulence) disappears. The blood pressure is recorded with the systolic pressure on top and the diastolic pressure below (for example 120/80 reads "120 over 80").

Emotional stress, excitement, exer-

cise, tobacco, anxiety, and meals may all influence blood transiently, necessitating multiple blood pressure determinations to establish an accurate estimate of the blood pressure. Thus, it is important to be as comfortable as possible when the blood pressure is measured, and to avoid eating or smoking for a half hour before the measurement. While everyone agrees that it is important to identify people with hypertension, it is just as important not to mislabel a person as hypertensive with normal blood pressure because of inaccurate equipment or poor measurement technique.

What are normal and abnormal blood pressures?

Over the past 15 years a number of important scientific studies have tried to determine the "safe" blood pressure, rather than "normal" blood pressure; this is because, in general, the lower the blood pressure the better — there is no precise distinction between normal and abnormal blood pressure. Between 1967 and 1970 the Veterans Administration reported the outcome of vigorously treating diastolic blood pressures between 105 millimeters of mercury (mm Hg) and 129 mm Hg. Stroke, congestive heart failure, kidney failure, and eye damage were significantly reduced. Recent studies have demonstrated a reduction in heart attacks even when diastolic blood pressures between 90 mm Hg and 104 mm Hg were vigorously treated. Based on this research, it is recom-

From the Moses H. Cone Memorial Hospital, Greensboro 27401-1020.

mended that, if possible, everyone's diastolic blood pressure be maintained ideally below 90 mm Hg.

We now know that the level of the systolic blood pressure is also an important risk factor for stroke and heart disease, but the benefits of vigorously treating systolic hypertension have not been as conclusively demonstrated as they have been for diastolic hypertension. A general recommendation is to maintain the systolic pressure below 140 mm Hg in males and 160 mm Hg in females (women are at lower risk, it seems, for health problems from systolic hypertension). Other important factors that increase the risk of heart disease include cigarette smoking, high blood cholesterol, and poorly controlled diabetes mellitus. All these risk factors are made much more dangerous by coexisting hypertension. Correcting each of these important risk factors is an effective means of reducing one's future risk of vascular disease. None of these corrections, however, has been proved to be as dramatically beneficial as normalizing persistently elevated hypertension.

In summary, there is no normal blood pressure — 140/90 (which everyone calls "normal") is really the highest blood pressure that is, in general, not associated with an increased risk of stroke, heart disease, and kidney disease. As in golf, the lower the better!

What actually causes hypertension?

Most people with persistently elevated blood pressure have no single or definable cause for their hypertension. It has been demonstrated that hypertensive people who are overweight can significantly lower their blood pressure by weight reduction, limiting dietary sodium, and increasing dietary potassium. Anxiety and nervousness, on the other hand, are not an important element in causing persistent hypertension and tranquilizers should not be used to treat hypertension. While many nervous people have high blood pressures, most do not, and it has never been

proved that anxiety causes blood pressure to be persistently elevated.

Rarely, a single cause for hypertension is discovered (for example, kidney disease or rare tumors) but this is the exception rather than the rule. Most people with high blood pressure have a genetic predisposition to hypertension (nearly all have a blood relative with high blood pressure, usually a parent or grandparent). The final "diagnosis" is idiopathic hypertension — idiopathic is a medical code word for "we don't know what really causes it, but we have to call it something."

How is hypertension treated?

The goal of therapy is to reduce the blood pressure, if possible, below 140/90. Successful therapy begins with education, because the health care provider and the patient must work as a team to achieve the therapeutic goal. Most people require exercise and dietary instruction to reduce their dietary salt intake and lose any excess body weight. A small percent of people with mild hypertension (diastolic blood pressures between 90-104 mm Hg) achieve satisfactory blood pressure control with these lifestyle changes. To normalize blood pressure, however, most hypertensive people also require medication.

Antihypertensive medication basically falls into three categories: the diuretics (for example, hydrochlorothiazide) which force the kidneys to eliminate excess salt and water; the vasodilators (for example, hydralazine) which reduce tension in the walls of blood vessels; and the sympatholytics (for example, propranolol or reserpine) which reduce the forceful beating of the heart. Ideally, the fewest number of medications which accomplish the job is best but occasionally two or three different medications are required in combination to reduce the blood pressure to an acceptable level. Before the effectiveness of a medication can be properly assessed, it must be taken as prescribed. Failure to take medica-

tion as prescribed is, by far, the most common cause for uncontrollable hypertension. Individualized therapy, motivated and knowledgeable patients, and a concerned health care provider are the main ingredients of successful therapy.

Can medication be harmful?

Any medication can have side effects that can range from mild and transient nuisances to intolerable toxicity. Before taking medication a person should know what side effects to expect and what to do if they occur. Diuretics can cause a fall in the blood potassium level with resulting muscle weakness. This can be minimized by reducing the amount of salt (sodium) in the diet. The blood potassium should be measured periodically while taking a diuretic. Vasodilators can cause palpitations (the sensation of excessively rapid beating of the heart) and weight gain from salt and water retention. To minimize the weight gain and increase blood pressure control, most vasodilators are combined with a diuretic. Sympatholytic drugs can cause drowsiness and lightheadedness upon standing which usually resolves after continued use. Individualizing therapy for hypertension means finding the most effective, least expensive, easiest to take medical regimen with the least side effects. Most over-the-counter medications (including aspirin, Tylenol, and cold remedies) can be safely taken with antihypertensive medication but if one is uncertain, the pharmacist should be consulted.

Does medication cure hypertension?

Medication unfortunately cannot cure hypertension. Taken as prescribed, however, medication can keep the blood pressure at the desired level, but this requires lifelong therapy in nearly all cases. Abruptly stopping anti-hypertensive medication can result in a rapid rise in the blood pressure to dangerously high levels occasionally requiring hospitalization.

Self-Help for High Blood Pressure

C. Stewart Rogers, M.D.

Most persons who have sustained hypertension will require lifelong therapy with one or more drugs. There are, however, millions of Americans with borderline or mild hypertension in whom the need for drugs is still controversial because of cost, uncomfortable side effects, and possible long-term harm. Even these mildly affected persons would benefit from lowering their blood pressure — but only if it could be done for a reasonable cost and without many side effects. There are also more people now who want to take as much responsibility as possible for their own health, and who are strongly motivated to use dietary or behavioral approaches to minimize the use of drugs.

There are several non-drug therapies that are known to have lowered the blood pressure successfully in many persons, but it is very important that interested patients understand the issues. These approaches are not easier than taking drugs, they are clearly harder. They may or may not be cheaper, and they may not be free of side effects, especially short-term discomforts. Most important, they may be insufficient to fully normalize the blood pressure, and thus may give false reassurance, especially if patients use initial success with these approaches as an excuse for dropping out of medical follow-up care.

On the plus side, anti-hypertensive methods like diet, exercise, and stress control may confer health benefits beyond blood pressure reduction. Some of the benefits for physical health are speculative, but there is strong indirect evidence that the cardiovascular system improves in efficiency and in resistance to the common degenerative diseases by these self-help programs. Most scientists

and other observers would agree that successful diet and exercise programs also confer psychological improvements in self-esteem and sense of well-being. By contrast, pills may cause modest reductions in metabolic and cardiac vigor, may impair sleep and mood, and may cause some persons to feel a loss of personal control or responsibility for their body.

The non-drug methods available for blood pressure lowering are behavioral and dietary. The first category has many techniques, ranging from simple relaxation to major life changes for stress reduction. In between are complex programs of meditation, serious exercise programs, and psychotherapy. Patients have a variety of motivations for undertaking behavioral treatment besides blood pressure reduction, and there may be many additional positive outcomes. But it is also clear that these approaches require tremendous commitments of effort, time, and other resources. Since there are so many behavioral approaches, and since most involve highly individual variations, the effects on blood pressure have been hard to study. The attempts that have been made have produced mixed and confusing results; each technique studied has achieved some successful outcomes in small numbers of highly-motivated patients. In most cases, however, it is impossible to assess the contribution of concurrent diet or other changes, and it is not known if the

reported blood pressure control is a long-term improvement.

Diet therapy has been somewhat easier to study and there is more confidence in the scientific medical community that weight control and salt restriction are effective treatments for hypertension. Obesity is commonly found in hypertensive patients, and substantial weight loss lowers blood pressure, often to normal. A successful weight control experience for an obese person is likely to be associated with other positive changes (exercise, self-esteem), and reducing the amount of food eaten usually reduces sodium intake as well.

Salt restriction is the most effective of all non-drug therapies, and was used successfully before any anti-hypertensive drugs were developed. Several cautions are in order: 1) only a small drop in blood pressure can be expected unless sodium restriction is severe, 2) not every patient will respond, and 3) the benefit lasts only as long as the diet is continued. On the other hand, Americans consume, on the average, over ten times the amount of sodium their bodies require for good health, and several times the amount consumed by some cultural groups in whom hypertension is unknown. A few simple changes in shopping and cooking habits can dramatically reduce salt intake; these need not involve strange or more expensive foods. The chart compares the sodium content of similar foods.

Comparison of the Sodium Content in an Average Serving of Common Foods			
Food	Sodium Content (mg)	Food	Sodium Content (mg)
Fresh pork (4 oz)	93	Ham (4 oz)	1,400
Fresh or frozen green vegetables	1-3	Canned vegetables	220-320
Orange juice (6 oz)	4	Tomato juice (6 oz)	650
Oatmeal	1	Boxed cereals	250-350
Apples, oranges, pears	2-3	Pickle (1)	1,000-2,000
Ground beef (4 oz)	76	Canned soup (1 cup)	850-1,100
Swiss cheese (1 oz)	74	American cheese (1 oz)	406

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Greensboro 27401-1020.

A serious attempt to lower sodium in the diet requires some effort and study. Pamphlets and low salt cookbooks are available from the American Heart Association or your local hospital dietitian. A low salt diet program is best approached as a deliberate plan for the whole family and should probably include some attention to reducing saturated fats and cholesterol, as well as increasing fiber. Most people will miss salt for a

time, and will be much happier if their diet plan includes experimentation with alternative spices. Salt-substitutes help some people tolerate low salt diets, and developing a taste for fresh fruits and snacks will go a long way toward meeting all healthy dietary goals.

Dietary changes, while not easy to accomplish, may be enough to avoid having to take drugs for mild or borderline hypertension, should reduce

the number or dosage of medications required in more serious hypertension, and will reduce the potassium loss in those who take diuretics for high blood pressure. Changes in dietary fat and fiber content will give benefits beyond blood pressure control, and other family members, especially children, may learn good habits that will ultimately prevent hypertension and other cardiovascular problems in themselves.

Varicose Veins

C. Stewart Rogers, M.D.

Long-standing problems with lower leg veins are very common among young and old alike, and may seem more serious to the patient than to the doctor. Most of the problems raised are cosmetic due to visible or bulging veins, bruising, or brownish splotches, but uncomfortable symptoms or serious skin breakdown often occur as well. Some of these problems respond well to surgery, but some do not, and it can be difficult to learn the best non-surgical ways to relieve symptoms.

First of all, we are talking about two different diseases that are only superficially alike. *Varicose Veins* are a simple disease of unknown cause, in which the veins just under the skin are bulging and very disfiguring. The disease is "simple" in the sense that the deep veins are usually normal, the blood drainage from the leg is adequate, and therefore the skin itself is not harmed. There can be some aching pain, especially after prolonged standing, but the chief problem is cosmetic.

The choice of therapy is also simple. For some patients long trousers or stockings may solve the cosmetic problems, and brief periods of rest

from standing may eliminate the pain. Support hose, even the routine store brands, may give added comfort. The only definitive treatment, however, is surgical removal of these superficial veins or injection of a solution that will scar them closed. This latter choice is not usually as successful in the long run, and is not available in many parts of the U.S.

The other disease is *Chronic Venous Insufficiency* which usually results from the damage left after an episode of blood-clotting in the leg veins (phlebitis). It may follow injuries or fractures, or occasionally it develops without a known cause. Basically the damage is to the mechanism that supports a smooth flow of blood uphill back to the heart, and results in much higher pressure in the veins. This, in turn, causes fluid to build up in the lower leg which leads to chronic skin disease with itchy rashes, discoloration, and ulcers. There may be a serious problem with pain on standing, described by patients as a "bursting" sensation.

Surgery will not improve this situation. Although at times the superficial veins are swollen to some degree, this is caused by malfunctioning deep veins that are beyond repair. This is a lifelong problem that cannot be cured, but it can be greatly re-

lieved in fairly simple ways. The problem is to reduce the pressure from within the veins, and to reduce the fluid accumulation in the ankles and legs.

Treatment requires a combination of leg elevation and high-pressure stockings. Elevation of the legs may be effective in mild cases if the patient can arrange the time necessary. The feet must be above the heart as long and as often as needed to control pain and swelling. Stockings are needed in most cases, and must be medical-strength (prescription) hose to overcome the abnormally high pressure in the veins. These may or may not require special fitting depending on the shape of the legs: what matters is firm pressure without a constricting band at the upper calf or thigh (which could make swelling worse and even cause phlebitis!).

Diuretics or fluid-pills usually do not help much unless there is another disease, like kidney or heart disease, contributing to the fluid. Persistent rashes or leg ulcers require special medical attention, but the mainstay of therapy is still reduction of pressure and fluids to allow normal healing. As in so many other chronic diseases, the patient has the major role to play in controlling symptoms and preventing complications.

From the Moses H. Cone Memorial Hospital, Greensboro 27401-1020.

Grass Roots Medical Journalism

Jack D. McCue, M.D.

STATE medical journals are caught in a pinch. Increasing competition from the popular "throwaway" journals makes it difficult for these modest publications to support themselves through advertising income, and the number of journals physicians receive through subscriptions and mass mailings makes most of us unwilling to pay for or even read yet another. Our state medical journal does serve special purposes, however, and we should be reluctant to let it go unread or simply atrophy — it keeps us in touch with our colleagues in other locations, and can inform us of medical, political, and social issues that are important to North Carolina physicians. Can we help make the *North Carolina Medical Journal* more worth the effort and expense?

Snappy covers, catchy titles, and readable articles that have special relevance to North Carolina physicians are an obvious response to making a state journal more popular — changes that have already been made with great energy and good results by Dr. Stead. The novel idea of including parts of a journal that can be left in the waiting room for patients to read is especially meritorious. Ultimately, however, a state journal will flourish or wither on the basis of its scientific, editorial, and historical content — articles with relevant, interesting information are required to keep it alive. A personal experience as guest editor of the *Maine Medical Journal* taught me some things that I thought might benefit the *North Carolina Medical Journal* — hence, this month's issue from Moses Cone Hospital.

All hospitals have repressed or budding scholars and researchers — innovation is not restricted to the ivory towers of academic medicine. Publishing insights from

one's practice experiences or the results of community hospital research, however interesting they may be, is another matter. It takes good writing skills, access to statistical analysis, a great deal of secretarial time, personal determination, good luck, and often an academic reputation to get case reports and studies published in refereed journals. To encourage practitioners in Maine to publish their shoestring research and case reports, the *Maine Medical Journal* decided to diffuse the responsibility for the monthly issues to the ten medical centers. Each major hospital was responsible for one issue of the journal yearly, and there was always a good soul who would take on the job of being guest editor to coordinate the efforts. The result was that each issue contained a yearly synopsis of the research and innovation from a different community hospital — valuable, often otherwise never-to-be published information.

Could the *North Carolina Medical Journal* use the multiple medical center (i.e., AHEC!) approach to medical journalism? Will someone in Wilmington, reading of Ms. Drainville's and Dr. Sevier's approach to diabetes education be inspired to start such a program? Will other neonatal ICUs look at the issues involved in preventing deafness, as Dr. Boer did? Will experienced practitioners reexamine their years of experience and record their clinical and philosophical insights that they have always intended to write down, as Dr. Freedman did?

Decentralizing the *North Carolina Medical Journal* to some degree might actually stimulate research, scholarly activity, and a greater awareness of the need to examine critically our own local experiences with medical care. It may stimulate readership because it would truly highlight what is happening in medicine in North Carolina — not just what is happening on the medical school campuses.

From Moses H. Cone Memorial Hospital, Greensboro 27401-1020.

Time Will Tell

Eugene A. Stead, Jr., M.D.

SHOULD Dr. McCue and I have accepted the paper by Arthur Freedman? He goes against conventional wisdom in stating that symptoms usually interpreted as resulting from the interaction of a normal brain with any adverse environment are in fact the output of an abnormal brain and that this output is relatively little influenced by environment. The only evidence presented is anecdotal and is based on his many encounters with complaining patients. I voted for acceptance because (1) it gives us a vignette of one person's view of North Carolina medicine; (2) all wisdom doesn't reside in medical centers; and (3) perceptive persons may lead the way for future scientists.

The tie between structure and function is of course obligatory. When two brains have different outputs, one can safely assume they have different structures. The cause of the difference is the question at issue. Conventional wisdom states that the structure of the complaining brain can be returned to normal by a variety of psychotherapeutic and environmental maneuvers. Freedman's experiences led him to believe that the abnormality is not reversible by these maneuvers and that the structure of the brain must be changed if its output is to be affected. He elects to change the structure by attaching chemical moieties to it.

We know from our experiences with diseases and drugs that the structure of the brain can be altered by adding or

removing materials that are too small to be detected by electron microscopy. The psychosis of Cushing's disease or myxedema is undoubtedly due to changes of this nature. Drugs causing changes in the outputs of the nervous system produce their effects by attaching to receptors in the nervous system in a way that alters their structure. Again, these changes in structure are submicroscopic.

My own bias is that Freedman will be proved correct in his thesis that the brains in his subsets of complaining patients are different from those of the non-complaining population. Contrary to him, I believe that the abnormalities in these brains are made obvious by environmental, cultural, and socioeconomic influences, and by the behavior of doctors who treat them in the framework of a variety of illnesses. There are many irreversible structural defects that become obvious only on appropriate testing. Color blindness, slow social learning, dyslexia, G6PD deficiency, and many allergies remain unknown by microscopic examination but become obvious by appropriate testing.

I am skeptical about Freedman's conclusions about therapy. I have regarded these persons as non-progressive variants from the average and have cared for them in the framework of health rather than illness. Time will tell which of us is correct.

Why Dependency Is Increasing

Eugene A. Stead, Jr., M.D.

THERE was a time when many believed that some combination of education, science and technology would reduce disability and make our welfare society a thing of the past. This is a dream that has not come true. What went wrong?

The stresses induced by independent living have exceeded the gains in performance produced by education. To function effectively in our increasingly complex society, each person has had to increase the number of persons with whom he interacts each day. Energy is lost in person-person interfaces and there are more opportunities for the development and expression of hostile feelings. Wear and tear on our bodies generated by hostile brains has a cumulative unfavorable effect on our bodies. This leads to illness and dependency.

The rate of change in our daily lives has increased with the progress of science and technology. Persons who could function independently in a simpler society have become dependent as their skills became obsolete early in their work life.

Our industrialized society has generated environmental hazards that increase dependency. Cigarette smoking, alcoholism, automobiles, machines that maim, asbestos exposure, drugs, air pollution, etc. have enlarged the rolls of the disabled and dependent.

Changes in social custom that permit males to renounce the lifelong support of their female partners and their children lead to dependency. This may in the end be the final straw that leads to complete socialism.

In his Special Article elsewhere in this issue of the *Journal*, Dr. Busse emphasizes yet another important factor creating more dependents — namely, aging. The optimist had hoped that when persons lived longer they could work longer. The data presented by Busse indicate that a decline in mortality does not necessarily signify a decline in work disability. In 1970, 15% of individual men between the ages of 60 and 65 were unable to work. In 1980 the figure had increased to 18.9%. In 1970, in the age group of 65-69 years, 21.9% were unable to work. In 1980 this figure was 25.2%.

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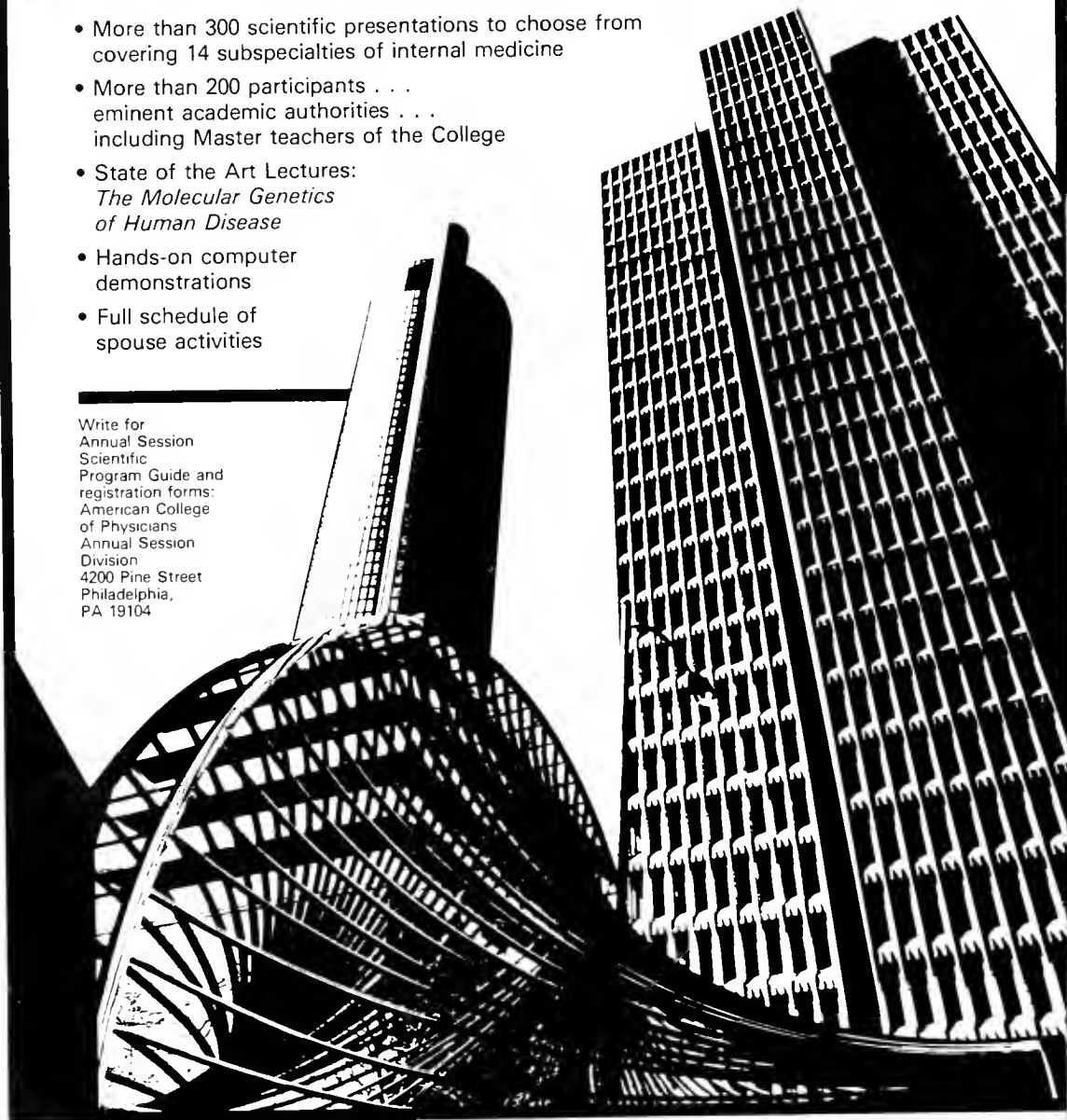
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Longevity, Disability, and Retirement

Ewald W. Busse, M.D.

THERE is a rapidly increasing number of people who are living longer than at any time in the past 2000 years. It is usually assumed that longevity is accompanied by a proportionate increase in the productive work years, followed by a period of retirement that is relatively free of disease and disability. This optimistic assumption has affected planning by both public and private committees and commissions. Unfortunately, evidence has existed for some time that the extension of life span in the United States and throughout the world has not been accompanied by a significant delay in the onset and the severity of chronic disease and disability. The assumption that improved health and a longer life span are synonymous has played a role in altering eligibility for Social Security benefits, other health and retirement plans and benefits, and the law by raising to 70 years the age for mandatory* retirement.

The National Commission on Social Security in its March 1981 report stated, "The Commission anticipates that increased longevity will be accompanied by a corresponding increase in active life." However, a minority of the Commission contended that "the evidence does not support any claims that longer life is equivalent to longer years in good health." A similar cautious view was expressed in the 1983 Report of the National Advisory Council on Aging of the National Institute of Aging.¹ According to the 1982 National Plan for Research on Aging, "There is no substantial evidence that the elderly of today have better or worse health than the elderly of yesterday."² Thus, the influence of Medicare is negligible. Although an optimistic viewpoint does have value, and it is quite possible that in the years ahead there will be improvement in the functional capacity of older people, this optimism, if not put in balance by reality, could result in poor planning for maintaining and improving the health and well-being of the elderly.

Life Expectancy

Life expectancy at birth is a prediction based upon assumptions, such as no major changes in the organization of medical care or preventive public health measures, no catastrophic change such as war or an epidemic, and no substantial change in environmental, social, or economic conditions. Life expectancy at birth in the USA in 1982 was 70.8 years for males and 78.2 years for females. A white male 65 years of age can expect to live 14.4 years, a female 18.8 years. The prediction for life expectancy in the year 2000 is 73.42 years for men and 81.05 years for women.

* Amended January 1, 1979, the Age Discrimination in Employment Act of 1967.

From the Department of Psychiatry, Duke University Medical Center, Durham 27710.

These changes in life expectancy are important for our planning but are likely to result in an overwhelming problem for the developing nations of the world.

The World Population

As of 1980, the U.S. population was 227,658,000 (Myers, 1983 [reading from material of the 1980 Bureau of the Census, personal communication]) and the total world population was estimated at 4.4 billion (4,432,100,000). Of this world population, 375,800,000 are 60 years of age and over; 45.4% are living in more developed nations, and 54.6% in less developed nations. By the year 2000 there will be a remarkable change. Only 39% of older persons will be living in developed regions and 61% in less developed regions. There will be an increase of over 200,000,000 old people in slightly fewer than 20 years. Of this increased number, 155,000,000 will be living in the less developed regions.

Male-Female Differences

Inasmuch as women outlive men, Feldman presents some very interesting data regarding the ability to perform specified activities.³ These include such things as the use of fingers, stooping, crouching or kneeling, carrying or lifting 25 pounds or more, or standing for long periods. The percentage of women between the ages of 35 and 65 that have difficulties with these activities exceeds that of men. Women use physicians and medical facilities more frequently than do men. Women have more minor disabilities than men, but have fewer major disorders that are life-threatening.

Changes in living habits could affect morbidity and mortality. The reduction in smoking and the improvement in personal health habits may alter the prevalence of disability and may change the mortality rates. Feldman refers to "the compression of infirmity." This is the hope of gerontologists who not only want to prolong life, but want to reduce infirmities so that the decline period preceding death will be shortened.

There are sex differences in the morbidity and mortality ratios in the three major cardiovascular diseases. These are coronary heart disease, hypertension, and vascular lesions of the central nervous system (stroke). In the U.S. coronary heart disease is the cause of death in twice as many men as women. Stroke is somewhat higher in men than in women, but hypertension is essentially the same for both sexes. These differences suggest that although there may be some causative factors in common between these three disorders, they are far from identical.

In the U.S. the high mortality of males compared to females appears to be a complex interaction between ge-

netically determined physiological differences, socioeconomic factors and cultural values. Behavioral expectations and environmental conditions may also be more dangerous for the man than for the woman.

Chronic Disease and Disability

Eighty-six percent of older people have some form of chronic disease. The most frequently recorded chronic conditions are arthritis, heart problems, hypertension, diabetes, brain impairment, and vision and hearing defects. However, only 5% of those not in institutions are housebound, and only 1% bed-ridden. The over 65 age group averages 16 days per year confined to bed. Most confinements in the older group are attributed to chronic conditions rather than to acute illnesses. Mental disturbances are common affecting approximately 10% of the population over 65 and 20% of those over 80. Of those in nursing homes, one-half suffer from some degree of intellectual impairment. In addition to organic brain disease, the most frequently reported mental conditions are chronic depression and anxiety.

To care for these increasing and disabling health problems, older people make more frequent use of medical services both as inpatients and as outpatients. They account for 15% of all doctors' visits, 25% of all prescriptions, and 34% of all days in short-stay hospitals. It is evident that older persons do suffer from acute disorders as well as exacerbations of chronic disorders, and these do require hospital attention. They are hospitalized for much longer periods of time than are young people, and surgical procedures have increased more among people over 65 than in any other age group.

Longevity and Disability

A National Survey of the Aged⁴ was conducted in 1962 and repeated in 1975. Medicare became effective in 1966; therefore, this report provided an opportunity to determine (1) whether Medicare affected how old people function, (2) how old people feel about their health, and (3) whether Medicare and other social programs of health services have made a difference in the provision of direct services to the elderly sick.

In this study an index of incapacity was developed. The old person was asked specifically: Can you go outdoors? Can you walk up and down stairs? Can you get about the house? Can you wash and bathe yourself? Can you dress and put on shoes? Can you cut your own toenails? The answers to these questions were scored on the basis of (1) without difficulty, (2) with minor difficulty, or (3) with the help of another person. In both 1962 and 1975 the proportion of those with no incapacities remained the same — 7 of every 10 were able to perform all of the tasks. However, there was a difference in that incapacitated elderly people were more likely to have seen a doctor in 1975 than in 1962. Six of every 10 had seen a doctor during the preceding month in 1975, five of every 10 in 1962.

Nursing Homes

Between 1974 and 1978, the number of nursing home residents increased by more than 21%. Some 20% of the aging will enter a nursing home before dying. It is projected

that nursing home residents will increase 54% by the year 2000. For persons 65 years of age and over, the median age in nursing homes was 81 in 1977. Forty percent of the elderly nursing home residents were 85 years of age and over. The ratio of women to men was approximately 3 to 1, and approximately 93.2% were white. Nursing home use is nine times higher among unmarried than among married elderly persons.²

Causes of Death

Since 1950 there has been a substantial shift in the ranking of the leading causes of death among those 65 years of age and over. In 1983, the major causes of death in this age group are listed as heart disease, malignant neoplasm, cerebrovascular disease (stroke), followed by influenza and pneumonia. Other frequently reported causes of death are arteriosclerosis, diabetes mellitus, and accidents. Although heart disease has declined, it remains the predominant cause of death and continues to increase with advancing age. Heart disease produces 51.5% of the deaths between 65 and 75 years, 61.1% between 75 and 84 years and 70% after the age of 85. In contrast, the percent of malignant neoplasms as a cause of death declines with advancing age. Malignant neoplasms produce death in 26.4% of those aged 65 to 74, 18% between the ages of 75 and 84, and 9.9% after the age of 85.^{5, 6}

The diseases listed as the most frequent causes of death in late life are often not the diseases that result in long term care. Other conditions such as arthritis and organic brain disease are the basis for serious disabilities.

Health and Retirement

The designation of a "normal" retirement age has been said to be the age at which people are no longer "sufficiently healthy to function in their jobs."³ Health status is a major consideration in flexible retirement, but mandatory retirement, usually at age 65, was not primarily linked to any functional capacity but rather to the size of the labor force and the economic situation.⁷

The prevalence of ill health and its effect on work incapacity is of major importance. The proportion of men in the 50-60 age segment who were unable to work because of illness increased between 1970 and 1980. In a more detailed breakdown, it appears that among individuals between the ages of 60 and 65, 15% were unable to work in 1970 and this increased to 18.9% in 1980. In the age group 65-69 years, 21.9% were unable to work in 1970 as opposed to 25.2% in 1980. Feldman presents other evidence that indicates that "a decline in mortality does not necessarily signify a decline in work disability."³

The question is, how did this paradoxical situation occur? The death rate from myocardial infarction has been declining in both men and women. However, because individuals with myocardial infarction are likely to have a number of other chronic disabilities, it is probable that eradicating death from myocardial infarction would increase the size of the pool of disabled survivors. The control of other diseases such as diabetes may also contribute to the increasing number of individuals with infirmities that limit activity.

The length of work years is affected by a number of

factors including health, socioeconomic class, and type and place of work. Those with less education are likely to be in more physically demanding jobs. Assuming that people become better educated, this would mean that there could be a decline in work disabilities. However, one also has to recognize that with changes in technology a substantial number of jobs will be more mentally and emotionally demanding. In the future psychological stress may play a significant role.

The 1979 law affecting mandatory retirement and raising the age for receiving maximum Social Security benefits is in part an attempt to reduce the deficit facing the Social Security system. A shift of just one year in the average length of retirement raises or lowers the Social Security deficit by nearly \$350 billion. There has been a steady increase in the number of retirement claims filed with the Social Security Administration by people who wish to retire between the ages of 62 and 64. Between 1947 and 1979, there was an important decrease in males 65 years of age and over who were continuing to work. Forty-eight percent of males over 65 were working in 1974. This had dropped to 20% in 1979. Working females 65 and over have remained at a constant 8%. The so-called dependency ratio, that is the ratio of people 65 and over to people aged 18-64, will continue to change. In the 1950s this ratio was 7.5 workers for every person retired. At present, there are approximately five active workers for every retired worker, but by the year 2030, this will be reduced to three workers for every retiree.²

Summary

Assuming that the number of elderly and their life expectancy continue to increase as predicted, and if disabilities are not considerably reduced from the current population, there will be a sizable segment of our population in the United States and throughout the world suffering from chronic disease and disability. To avoid further demands on already overburdened resources and a reduction in the quality of life, immediate and substantial investigations must be undertaken.⁸ Research is needed to identify the causes of chronic disease and to develop preventive measures, treatment, and rehabilitation.

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Q: Elevated Serum Creatine Kinase (Does/Does Not) Equal Myocardial Infarction?

Linda M. Frazier, M.D. and Francis A. Neelon, M.D.

A. Not all that glitters is gold. Likewise, not all patients with elevated serum creatine kinase (CK or "CPK") are having a myocardial infarction. The following case shows how physicians can be fooled:

A sixty-one-year-old woman with a long history of manic-depressive disorder was admitted to a local hospital because of marked paranoia and hostile behavior. A routine chemistry profile revealed a CK of 718 mIU/ml (normal: 25-235) with a muscle-brain (MB) fraction of 6.4 percent (normally not present), but she denied chest pain and had no history of heart disease. There were no cardiopulmonary abnormalities on physical exam. She was transferred to the coronary care unit and treated for an acute myocardial infarction. CK rose over the next two weeks to 1040 mIU/ml but CK-MB fell to 0 percent. Lactate dehydrogenase isoenzyme II was never elevated, varying from 27 to 33 percent (normal: 29-37). Electrocardiograms were normal except for nonspecific ST-T changes.

Subsequently, serum thyroxine was found to be 2.3 µg/dl (normal: 4-12) with a triiodothyronine resin uptake of 30 percent (normal: 34-44). Although these values are consistent with thyroid gland failure, the thyroid stimulating hormone (TSH) of 2.7 µIU/ml was not appropriately elevated (normal: less than 6.5). No endocrine diagnosis was made and she was transferred to Duke University Medical Center for treatment of her psychiatric condition and further evaluation of her thyroid disorder.

She denied cold intolerance; there was no change in hair or skin texture or in bowel habits. She was somnolent but oriented. Visual fields were normal; skin was dry; there was no edema. She was diffusely weak; tendon reflexes were absent. CK was 443 U/l (normal: 20-120).

On the basis of the clinical exam, she appeared to be hypothyroid in agreement with her depressed thyroxine and triiodothyronine resin uptake. But her TSH was not elevated. Primary hypothyroid patients with a normal hypothalamic-pituitary axis produce marked elevations in TSH in an attempt to stimulate the secretion of more thyroid hormone. We suspected that the patient had pituitary failure, and carried out a battery of pituitary function tests.

To test the ability of the pituitary to secrete TSH, we gave intravenous thyrotropin releasing hormone (400 µg). The results showed that the pituitary was not functioning

properly because TSH did not rise above 5.1 µIU/ml from a baseline of 4.8 µIU/ml (normal response: greater than 6).¹ Nor was the pituitary able to produce adequate levels of gonadotropins: follicle stimulating hormone was 7.0 mIU/ml and luteinizing hormone was 6.3 mIU/ml (normals for postmenopausal women: greater than 40 mIU for both hormones).

In order to test pituitary production of adrenocorticotrophic hormone (ACTH), adrenal cortical function was first assessed by a cosyntropin stimulation test. We gave intravenous cosyntropin (250 µg); the patient's adrenals produced a prompt and normal rise in serum cortisol to a peak of 65.3 µg/dl. Then, the ability of the pituitary to stimulate adrenal cortisol production (i.e., to secrete ACTH) in response to stress was measured. We gave regular insulin (0.1 U/kg body weight) intravenously to create hypoglycemic stress. Serum glucose fell to 35 mg/dl (normal: 75-110), but serum cortisol only rose to 7.7 µg/dl from a baseline of 6.3, indicating pituitary ACTH dysfunction (normal response: cortisol rise over 15).



Figure 1. Computerized tomography of the patient's sella turcica. This is a coronal section of a contrast study. The ventricles are visible at the top, and the arrow points to the pituitary fossa. The material in the fossa is of the same density as that in the ventricles, consistent with "empty sella."

From the Department of Medicine, Duke University Medical Center, Durham 27710.

These studies document panhypopituitarism preventing the patient from producing adequate levels of TSH, gonadotropins or ACTH. Computerized tomography of the sella turcica (figure 1) was consistent with "empty sella." Since empty sella is a benign anatomical variant, this finding cannot explain the pituitary dysfunction and further evaluation is planned. Meanwhile, she was begun on cortisone acetate and thyroxine replacement and serum CK fell.

This patient has an unusual type of hypothyroidism due to generalized dysfunction of the pituitary gland. Her hypothyroidism undoubtedly caused the elevated CK since elevated CK levels are found in the serum of 66 percent of hypothyroid patients. The degree of elevation is related to the duration and severity of hypothyroidism. The elevated CK is felt to originate in muscle, because it is primarily of the muscle-muscle (MM) fraction, and because hypothyroidism is often accompanied by a neuromyopathy. Nevertheless, two-thirds of hypothyroid patients do have mildly elevated CK-MB fractions, ranging from 0.8 to 13 percent of total CK. This may be due to a mild cardiomyopathy, known as "myxedema heart." Sixty percent of hypothyroid patients also have elevated serum aldolase activity.²

There are other important causes of elevated serum CK which can lead to an incorrect diagnosis (table 1). Skeletal muscle trauma, seizures, rhabdomyolysis, myositis, and muscular dystrophy can elevate serum CK activity.³ Alcohol intake can raise serum CK; elevation is mild in chronic alcoholism, modest with acute intoxication, and may be very high in delirium tremens. Muscle biopsy may show degeneration and necrosis when acute alcohol intoxication is accompanied by muscle pain and swelling.⁴ Concomitant alcohol use may account for the elevated CK seen in some acutely psychotic patients, although others suspect the enzyme may be released from the brains of psychotic patients.⁵ Elevated CK can be seen in brain injury such as

Table 1.

Causes of Elevated Serum Creatine Kinase other than Myocardial Infarction

Hypothyroidism
Skeletal muscle trauma
Intramuscular injection
Seizures
Rhabdomyolysis
Myositis
Muscular dystrophy
Alcohol use
"Psychosis"
Cerebrovascular accident
Encephalitis
Brain tumor
Subdural hematoma

cerebrovascular accident, encephalitis, tumor or subdural hematoma. Interestingly, CK-MM is the predominant isoenzyme seen, perhaps because the brain-brain fraction has a brief half-life.

The astute physician must not be lured into making a diagnosis of acute myocardial infarction by a glittering CK on a chemistry profile when any of these other disorders are present.

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Rocky Mountain Spotted Fever in Pregnancy

Harry A. Gallis, M.D., R. Christopher Agner, M.D. and Carroll John Painter, M.D.

IN a recent review of Rocky Mountain Spotted Fever (RMSF) in pregnancy,¹ and in a review of the medical literature through mid-1983, we found no reported clinical experience with RMSF in pregnancy. Since over half of the cases of Rocky Mountain Spotted Fever occur in individuals under the age of 40, it is surprising that it has not been seen in combination with pregnancy. Two of us (RCA and CJP) encountered the following patient in the summer of 1983.

The patient was a 19-year-old caucasian woman in her first pregnancy who noticed and removed an embedded tick on July 31, 1983. Three days later when she was seen at a routine prepartum visit, asymptomatic pyuria was noted, and she was begun on Nitrofurantoin. Five days later she developed a temperature of 101° and her prescription was changed to ampicillin.

Physical examination was remarkable for blood pressure 120/70, pulse 100, mild anxiety, abdominal examination consistent with 34 weeks gestation, and a macular rash over the arms, legs, and upper trunk, with several petechiae on the palms, soles, and upper arms.

The white blood cell count was 8,600 with 58 polys and 20 stabs, with a hemoglobin of 11.5 gms% and a platelet count of 122,000. The electrolytes showed a sodium of 139 mEq/liter, potassium 3.7 mEq/liter, chloride 102 mEq/liter, and CO₂ of 20 mEq/liter. The initial VDRL and Weil-Felix titers were negative.

We diagnosed possible RMSF and started her on intravenous chloramphenicol, 500 mg every 6 hours on August 11, 1983. Within 72 hours she was afebrile. Chloramphenicol was administered by mouth at the same dosage on the 3rd through the 5th day and then was discontinued.

The following acute and convalescent titers for RMSF were obtained:

Dates	8/12/83	8/25/83
Proteus OX 2	Negative	1:20
Proteus OX 19	Negative	1:640
Proteus OX K	1:40	1:40
Indirect hemagglutination	less than 1:16	1:1,024

These titers are interpreted as diagnostic of acute Rickettsial infection.

Our patient made rapid clinical improvement and completed the rest of her pregnancy, delivering a healthy 5 pound 7 ounce female infant with an Apgar score of 9/9 on September 10, 1983. Complete blood count on the mother at the time of delivery was normal. Complete blood count on the infant revealed a white blood count of 28,300 with 76 polys, 18 lymphs, 5 monos, and 1 Eo. The hemoglobin was 24.7, hematocrit 68, and the platelet count was 161,000. The reticulocyte was 6.6%. The mother and in-

fant were reported well 2 months following delivery.

Rocky Mountain Spotted Fever represents a challenge to the clinician in that diagnosis usually must be made on clinical grounds. In endemic areas such as North Carolina, the two most confounding illnesses are perhaps influenza in the early spring and enteroviral (aseptic) meningitis in the late summer and early fall. Fever, myalgias, and headache may also be early manifestations of other illnesses and may be further confused by the occurrence of skin rash (e.g., measles, infectious mononucleosis, toxic shock syndrome, meningococcemia, other bacteremias, leptospirosis, etc.). The mild CSF pleocytosis that occurs in some patients with RMSF may be equally confounding.

The only specific test for RMSF early in its course is a skin biopsy stained with fluorescent antibody for *Rickettsia rickettsiae*.² This test is positive in over 80% of the cases. If this test is negative or unavailable, patients must be treated empirically depending upon the physician's degree of suspicion of RMSF. Definitive diagnosis therefore must be made by retrospective serology, as it was in our case.

The drugs of choice for all Rickettsial diseases are either tetracycline (30 mg/kg per day in divided doses), doxycycline (100 mg twice daily for the first day followed by 100 mg per day), or chloramphenicol (50 mg/kg/day in divided doses). Since tetracycline and doxycycline are *contraindicated* in pregnancy, suspected or skin biopsy proven cases should be treated with chloramphenicol. Therapy is usually continued for 7-10 days, or for 5 days after defervescence. Blood counts should be monitored every few days during treatment, although adverse effects of chloramphenicol are not usually seen in courses of short duration. Adverse fetal effects may be seen if term delivery is precipitated in the presence of high blood levels.

Since there are no previously reported cases of RMSF during pregnancy, one can only speculate as to the potential effects of this infection on the fetus. In severe cases vascular involvement of the placenta could lead to fetal compromise or premature precipitation of labor. A major adverse effect of RMSF might result from its treatment if tetracyclines were inadvertently used during any state of pregnancy. In the first trimester, limb hypoplasia secondary to abnormal osteogenesis may occur.³ Dentition may be damaged when the crowns of the teeth are developing in the second and third trimesters.⁴ In addition, intravenous doses given in the last trimester may cause hepatic failure or pancreatitis in the mother.

On the other hand, chloramphenicol has no more untoward effects during pregnancy than in ordinary use in adults.⁵ The drug crosses the placenta in 30-80% of maternal blood levels and there is no known teratogenicity. If given near delivery, however, the gray baby syndrome, a

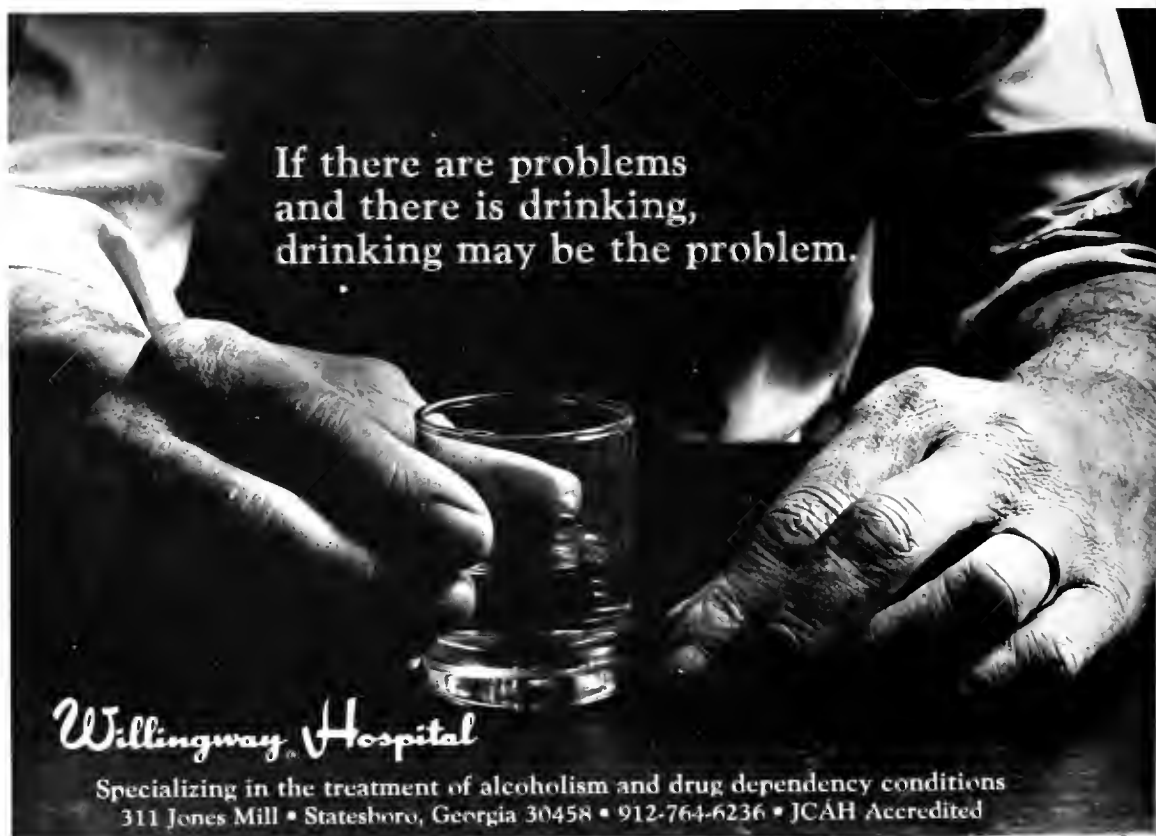
severe reaction to the drug, may occur. Therefore, this must be weighed against the potential toxicity of tetracyclines or the likelihood of imminent delivery.

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Recent Rulings of the North Carolina Board of Nursing

Hettie L. Garland, R.N.

THE Joint Practice Committee of the North Carolina Medical Society and the North Carolina Nurses Association, in keeping with its objectives to improve communication between nursing and medicine to advance joint planning and action, and to serve as a liaison between the two official parent organizations, requested and received approval from the North Carolina Board of Nursing to regularly publish rulings of the Board that may affect the practice of nurses and physicians in a variety of settings. The North Carolina Board of Nursing regularly publishes the *Bulletin* as a mechanism of disseminating rulings and interpretations as well as other information to registered nurses and licensed practical nurses in the state. However, this information is not always transmitted to physicians and other personnel with whom nurses work. The information contained in this article is excerpted from the *Bulletin* published by the Board of Nursing in September 1983.

The nurse members of the North Carolina Board of Nursing are nominated and elected by the licensees in the state. In addition, two public members are appointed by the Governor. The current membership of the Board follows:

R. Leigh Andrews, RN, Chapel Hill
Sarah Pike Brown, RN, Raleigh
Joyce M. Gainey, RN, Winston-Salem
Olga C. Hoskins, RN, Lenoir
Susan M. Kennerly, RN, Concord
Sharon T. Sells, RN, Stanfield
V. Elizabeth Berryhill, RN, Greenville
Ernestine B. Small, RN, Greensboro
Russell E. Tranbarger, RN, Greensboro
Nancy V. Cook, LPN, Mocksville
Sammy K. Griffin, LPN, Burlington
Christine G. Jones, LPN, Chapel Hill
Betty H. Hunt, LPN, Asheboro
Donna S. Thigpen, Public Member, Beulahville
Joseph H. Nanney, Public Member, Clyde

The following are actions of the Board at the September 1983 meeting:

1. ruled that the removal of suction wound drains upon the order of a physician is within the scope of nursing

practice for registered nurses and licensed practical nurses.

2. ruled that the insertion of enteral feeding tubes and other tubes with mercurial bulbs is within the scope of nursing practice.
3. ruled that the insertion of intravenous catheters of lengths no longer than 1½ inches is within the scope of nursing practice for a licensed practical nurse.

In addition, the Board ruled that the following are within the scope of nursing practice for a registered nurse and/or a licensed practical nurse provided that the Board of Nursing has been notified that there is 1) a written protocol, 2) documentation of appropriate training and supervised clinical practice, and 3) written approval of nursing administration, agency administration, and medical staff within the agency:

1. bimanual pelvic and rectal examination is within the scope of practice for a registered nurse.
2. insertion of fetal scalp electrodes is within the scope of nursing practice for a registered nurse when the membranes are ruptured spontaneously or by a physician.
3. removal of a thoracotomy tube is within the scope of nursing practice for registered nurses and licensed practical nurses.
4. administration of subsequent doses of epidural anesthesia is within the scope of nursing practice for a registered nurse.

The North Carolina Board of Nursing celebrated its 80th anniversary on March 3, 1983. North Carolina has the distinction of being the first state to provide for the registration of nurses: on March 3, 1903, then Governor Charles B. Aycock signed the bill establishing the Board of Examiners of Nurses. Over the years since 1903, the statute has been amended and revised. The current nursing practice act became effective July 1, 1981. North Carolina also has the distinction of being the only state that provides for the nomination and election of its nurse members by the licensees in the state.

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Build A "Beta" Mousetrap — Propranolol Poisoning

Ronald B. Mack, M.D.

FOR Heaven's sake why do we need beta blockers — Can't we just leave the betas alone!! Almost everything we read today is negative, e.g., starch blockers, field goal blockers, alpha blockers and of course beta blockers. Are "betas" so bad that we have to block them?

Well, it's a long story, but it's basically a lesson in communication. In any good communication system there should be a *sender* and a *receiver* (AKA receptor). Motor nerves communicate information/instructions from the nerve action potential (sender) to the effector, e.g., cells, muscles, nerves, or glands (receptor), via chemical transmitters. These chemical transmitters can affect the receptor in several ways, i.e., as agonists, partial agonists, blockers, or no measurable effect. The *agonist* has an affinity for the receptor and its purpose is to cause the effector cells to do what they do best; to perform in their characteristic fashion. A *blocking agent* also has an affinity for the receptor but does not cause the receptor cells to do their "number." Is this getting too muddled? Look, it is really quite simple. Let me give you an example: I walk into a restaurant in the North End in Boston and my nasal *sensors* pick up the odor of linguine with white clam sauce. I am *agonizing* to receive this delightful dish. My neurotransmitters are really excited — I am salivating, my heart rate increases, my pupils get large, but there is a long line of fellow trenchermen and trencherwomen ahead of me — I am *blocked*.

The peripheral nervous system has two main transmitters that we know about: (1) *acetylcholine* — nerves using this chemical are called cholinergic, (2) *catecholamines* (e.g., norepinephrine, epinephrine, dopamine and isoproterenol) — nerves using these compounds are called *adrenergic*. The adrenergic receptors are further classified into *alpha* and *beta* types. Alpha receptors are primarily excitatory and their stimulation produces vasoconstriction, decreased GI motility, pupillary dilatation, "gooseflesh" and uterine contraction of the gravid uterus (only in women). The *beta* receptors are what we are about in this exercise. They are mainly inhibitory and are found in the heart, blood vessels, GI tract and bronchi. There are two beta receptors that we are concerned about: *beta-1* receptors predominate in the heart and stimulation of these receptors causes tachycardia, an accentuation of AV conduction and cardiac contraction, thus positive chronotropic (rate) and positive inotropic (force) action. *Beta-2* receptor stimulation causes vasodi-

lation, increased GI motility, bronchodilatation, glycogenolysis and hyperglycemia. Well then, *beta blockers* should reverse these effects. Beta-adrenergic blockers are simply competitive inhibitors of catecholamine binding at beta-adrenoreceptor sites. They decrease the effect of a catecholamine agonist on a sensitive receptor tissue. (The cheerleaders now begin the familiar chant — "Block those betas," etc.)

Propranolol (Inderal) is the potential toxin that is the real reason behind this use of lengthy explanations. This drug is one of the most popular of written prescriptions in the United States. Because of its widespread availability overdoses are relatively common. There are plenty of beta blockers on the market but this discussion will be limited primarily to propranolol overdose. Propranolol is a non-selective beta blocking agent, i.e., it blocks both beta-1 and beta-2 receptors (I love it when a drug is not prejudiced). It is currently being prescribed for the amelioration of hypertension, thyrotoxicosis, arrhythmias, angina pectoris, hypertrophic subaortic stenosis as well as the prevention of common migraine headaches. Many physicians use this drug in the treatment of severe overdose situations such as with phenylpropanolamine, cocaine or PCP intoxications where hypertension and cardiac arrhythmias are often very troublesome.

Speaking of pharmacokinetics (who brought that up?), propranolol (Inderal) is a weak base with a pKa of 10.4, is 93% protein bound with an apparent volume of distribution of 3.6 l/kg (well, that pretty well eliminates any thoughts of dialysis in overdose situations!). This drug is quite lipid soluble; so much so that it rapidly crosses the blood brain barrier and accumulates in the brain. Propranolol is quite rapidly absorbed from the GI tract. When taken orally about 90% or more is absorbed, but probably only 30% reaches the systemic circulation because the liver exacts a tribute via first pass hepatic elimination. The liver, in fact, almost completely metabolizes Inderal (99%); the rest is eliminated by the kidney. In patients with normal kidney function the peak serum concentration is reached in 1-3 hours whereas the $T_{1/2}$ is 2-3 hours in patients who have normal liver function. However, it must be emphasized that in an acute oral overdose situation the $T_{1/2}$ may be prolonged.

I suppose that now that we know what beta-1 and beta-2 stimulation produces and also what the blockers (AKA antagonists) do we should be able to figure out what an overdose of propranolol produces in the patient. (Maybe you can; I cannot, so let us proceed.) Adverse clinical

From the Department of Pediatrics, Bowman Gray School of Medicine, Winston-Salem 27103.

features following an acute oral overdose can appear in as early as 20 minutes post ingestion but more typically occur in 1-2 hours. There does not appear to be a great deal of clinical correlation between the serum propranolol concentration and its effects on the patient; however, serum concentrations > 1500 ng/ml often are associated with big trouble and concentrations > 14,000-28,000 ng/ml have been associated with fatal outcome. The two main features of a large propranolol overdose are *hypotension* and *bradycardia* but *low cardiac output failure* and *cardiogenic shock* are very real possibilities. Needless to say, the patient's before-ingestion cardiac status is an important variable in the assessment of an overdose. It is not too difficult to imagine a person with heart disease (and who has a propranolol supply) becoming depressed and taking a whole bottle of this stuff. In patients with underlying cardiac disease *pulmonary edema* is another real possibility. The patients with pre-existing bronchospastic disease are apt to experience a fair amount of *bronchospasm* following lnderal overdose. *Coma*, *convulsions* and *respiratory depression* can also occur. In my opinion, one of the most interesting clinical features of propranolol overdose is *hypoglycemia*. It is known that this drug has the ability to interfere with the glycogen mobilizing effects of catecholamines. Apparently this hypoglycemic potential is a problem limited to children and probably diabetics.

In the management of a patient with a propranolol overdose in terms of severity a good history and physical are a must. The EKG findings can vary from a 1st degree AV block (\uparrow P-R interval) and sinus bradycardia to a complete disappearance of P waves, QRS widening (intraventricular conduction defects) and an old nemesis, asystole. A chest x-ray can reveal the presence of pulmonary edema. It would be wise to order blood glucose and serum potassium levels (hyperkalemia can be reported in some of these patients).

In our experience with the propranolol overdose situation most of the patients require rather careful observation but not much more; maybe we have been lucky so far. As in dealing with other potentially lethal toxins expect the worse but *only treat the patient not the poison*. As a general rule, the commonest causes of death in victims of *any poison* are cardiopulmonary in origin whether secondary to the direct effects on the circulation and lungs or secondary to CNS effects. Therefore, it is no surprise that the principal complications are arrhythmias, hypotension, shock and pulmonary edema. As we have seen, propranolol can produce all of these evil conditions if consumed in excess.

Following an acute overdose, gastric emptying should be performed followed by the administration of activated charcoal and a saline cathartic. *Hypotension* can be caused by the bradycardia or from the depression of myocardial

contractility or a CNS effect. If the hypotension is severe enough to require treatment, place the patient in the Trendelenburg position and administer fluids if they are indicated. If there is *sinus bradycardia* and *hypotension*, *atropine* seems to be the treatment of choice. If the atropine fails, *isoproterenol* is the next drug to use. Isoproterenol is often required in rather large doses because of the competitive blockade with the beta blocker. Some authors would use dopamine here if the systemic vascular resistance was low and would use dobutamine if the systemic vascular resistance was normal or high. Intracardiac pacing can also be tried. Apparently in *sinus bradycardia without hypotension* no specific treatment may be necessary; it all depends on whether the cardiovascular status is impaired or not. *Convulsions*, other than those caused by hypoglycemia, usually respond to intravenous diazepam (if diazepam fails, give phenytoin).

Glucagon appears to be able to play a decisive and fascinating role in the management of severe propranolol overdose. Glucagon, because it acts at a site quite distant from the beta receptor, activates myocardial adenyl cyclase thus stimulating cyclic AMP synthesis and resulting in cardiac effects similar to beta-adrenergic agonists. Simply stated, glucagon can increase myocardial contractility and heart rate (inotropic and chronotropic effect) despite high circulating concentrations of beta blockers. The effects of a single dose of this drug can produce a dramatic response in 5-10 minutes lasting for 15-30 minutes; if it works in your patient you may want to begin a constant infusion (watch out for emesis and hyperglycemia). Obviously if the patient is hypoglycemic intravenous glucose is the order of the day.

Because so little of the parent drug is excreted unchanged in the urine (less than 1%) forced diuresis is not a good idea and this method can also overload the cardiopulmonary apparatus. The large amount of protein binding and volume of distribution of 3.6 l/kg sort of eliminates the use of dialysis to rid the body of this drug. It is quite encouraging to note that although severe propranolol overdose situations can and do occur, most of your patients will only require gastric decontamination and monitoring.

At the request of the women in my family — a considerable number I might add — my grandson and I are experimenting with the possibility of discovering *theta blockers*. Both he and I suffer from *SMD* which we believe is caused by stimulation of *theta agonists*. SMD is Selective Male Deafness. In this disease certain sounds of specific decibel and frequency emitted by the female voice (grandmother, mother, wife, sister, daughter, colleagues, etc.) are selectively not heard. It can be a devastating illness and has millions of sufferers in this country.

What State Societies Are Talking About: The Resolutions Presented to the AMA House of Delegates at the December 1983 Meeting

Resolutions

1. Nursing Homes — Quality of Care, Medical Staffs and Ancillary Personnel
2. Development of National Policy for Immunizations and Vaccine Development
3. Use of the Choke and Sleeper Holds in Prisons
4. Scientific Accuracy in Racial, Ethnic and Religious Designations in Medical Records
5. Restudy of the Selective Draft of Physicians
6. Support of Individualized Medical Care
7. Amendment to IRS Code to Extend to Physician-Owned Mutual Protective Trusts the Same Tax Benefits as Physician-Owned Liability Insurance Companies
8. Contract Arrangements
9. Reimbursement Systems for Physicians Services
10. Life-Sustaining Medical Treatment (Constitution and Bylaws)
11. Physician Conflict of Interest (Constitution and Bylaws)
12. Regulation of Self-Insured Medical Plans
13. Cessation of Vaccination Program for Smallpox
14. Status of House Speaker and Vice Speaker (Constitution and Bylaws)
15. Preserving the Physician/Patient Relationship (Constitution and Bylaws)
16. Sale of Donor Organs for Transplant (Constitution and Bylaws)
17. Physician Training for Management of Injuries Encountered in Nuclear Explosions
18. Equity in Tax Exemption
19. Patient Medication Instruction (PMI) Sheets
20. "Opium" Perfume
21. Formaldehyde in Manufactured Housing
22. AMA Election Process — Campaign Expenses
23. Care of Handicapped Newborns in Hospitals
24. Poison Control Centers: Computer Linkage for the Dissemination of Information
25. A Mechanism to Correct the Current Discrimination Against Children in Health Insurance
26. Updating of Veterans Administration Rating Schedule
27. Prospective Reimbursement of Hospitals (DRGs) — Ethical Implications (Constitution and Bylaws)
28. Use of AMA CPT-4 by HCFA
29. Organized Self-Governing Medical Staff
30. Prohibition of Military Physicians Serving in Managerial and Administrative Positions
31. 500 Gram Determination for Fetal Births
32. Medicare Preauthorization Review
33. Affirmation of Pledge to Reduce Deaths and Injuries Caused by Drunk Driving
34. Free Competition in Medicine
35. Therapeutic Substitution
36. Peer Review of Medical Fees
37. Publicizing AMA Position on Bioethical Issues (Constitution and Bylaws)
38. Physician Participation in Preferred Provider Organizations
39. Mandatory Medicare Assignments
40. Prospective Payment for Medicare Medical Services
41. Commendation of Motor Vehicle Manufacturers Association, et al.
42. Public Health and Safety Awareness
43. State Society Medical Staff Sections
44. AMA House of Delegates Procedures
45. JCAH Medical Staff Standard
46. Implementation of Smoke Free Society by the Year 2000 within the AMA
47. Development of a Medicare Prospective Payment Pilot Program for Physicians
48. Low Level Radioactive Waste Disposal
49. Direct Advertising of Prescription Drugs to the Public by the Pharmaceutical Industry
50. The Immediate Emergency Care of Critically Wounded Military Servicemen

"Adequate Benefits" in Employer-Offered Health Services

I always enjoy reading the papers submitted by the Council on Medical Services to the House of Delegates. The report on "Adequate Benefits" in Employer-Offered Health Insurance is of interest to all doctors. The Council recommends that an employer would be entitled to take premium payments as a tax deductible business expense only if his health insurance programs provided these "adequate benefits." In order to be judged an "adequate benefits" plan and qualify for tax deduction, the plan would have to meet only two basic requirements:

- (a) It would have to provide some extent of coverage for all services listed in Appendix A.
- (b) It would have to limit the beneficiary's cost-sharing for covered expenses to a specified maximum of \$2,300/person, with this amount updated yearly.

Appendix A Insurable Health Expenses

- A. *Diagnostic, Therapeutic or Preventive Medical Services Provided by or Under Direction of Licensed Physicians in the Office, Hospital, or Other Setting*
 - 1) Diagnosis and Medical or Surgical Treatment of Illness or Injury
 - 2) Psychiatric Care
 - 3) Diagnostic X-ray and Laboratory Services
 - 4) Radiation Therapy
 - 5) Consultation
 - 6) Pre- and Post-Natal Care of Mother and Infant, including delivery
 - 7) Periodic Medical Examinations: 6 visits per dependent per year for first year of life, biannually for ages 2-21, every 5 years for ages 22-40, every 2 years for ages 41-65
 - 3) Immunizations Which Are Cost-Effective for the Beneficiary Group Covered
- B. *Emergency and Outpatient Services for Physical and Mental Illness*
 - 1) Outpatient diagnostic services (x-rays, lab tests, etc.)
 - 2) Use of operating, cystoscopic, cast rooms and supplies
 - 3) Use of emergency room and supplies for emergencies
 - 4) Ambulance services
 - 5) Treatment for alcoholism
- C. *Inpatient Hospital Care for Physical and Mental Illness*
 - 1) Bed, board and nursing services
 - 2) Drugs, oxygen, blood, biologicals, supplies, appliances and equipment used in the facility
 - 3) Operating, delivery, recovery room charges; intensive, coronary, special care, rehabilitation unit charges
 - 4) Diagnostic services (x-rays, laboratory tests, EKGs, etc.)
 - 5) Care for pregnancy and complications
 - 6) Physical, occupational, speech therapy
- D. *Inpatient Skilled Nursing Facility Care for Physical and Mental Illness*
 - 1) Bed, board and skilled nursing
 - 2) Physical, occupational, speech therapy
 - 3) Drugs, biologicals, supplies or equipment used in the facility
- E. *Home Health Services by a Certified Home Health Agency as Ordered by a Physician*
 - 1) Nursing care
 - 2) Physical, occupational, speech therapy
 - 3) Medical supplies and appliances (other than drugs and biologicals)
 - 4) Rental of durable medical equipment
 - 5) Oxygen, blood, biologicals

The Council believes that this approach has several major benefits: (1) it allows easy comparability of policies against the standards; (2) rather than attempting to come up with a "laundry list" specifying the amount of each service to be covered, it permits the buyer and seller to negotiate the extent of coverage for the required services — while requiring *some* extent of coverage for all of them and setting a limit on the beneficiary's cost-sharing for covered expenses; and (3) it presents an approach with which the insurance industry is familiar and for which premiums can be determined without significant difficulty.

The Council discusses the standards for adequate benefits under four headings:

Standards for "Adequate Benefits"

- 1) The plan would provide some extent of coverage for all of the health services listed in Appendix A.
- 2) Some degree of beneficiary cost-sharing for covered expenses would be required up to a specified per-person limit beyond which no further beneficiary cost-sharing

for covered expenses would be required. The cost-sharing limit would be the same for all subscribers and should be set at 10% of the national median family income rounded to the nearest \$100 — and updated yearly. Based on current data, the per-person cost-sharing limit would be \$2,300.

- 3) There would be no maximum limit — either lifetime or per episode — on the amount paid by the plan for covered expenses in the catastrophic portion of coverage.
- 4) In paying for physicians' services, the amount allowed toward meeting the beneficiary's cost-sharing limit would be the difference between the plan payment and the 90th percentile of physicians' customary or median charges in the area (the amount which would cover the customary or median charge for a service at least 90% of the time it is performed). Once the cost-sharing limit was reached, the plan would pay the 90th percentile of customary charges in full. The plan would continue to pay for hospital expenses on a service basis, with contractually specified beneficiary cost-sharing being applied toward the cost-sharing limit.

Cost

The estimated annual premium costs for a plan meeting these adequate benefit standards (coverage for the services specified in Appendix A and a cost-sharing limit) are displayed in Appendix B. These estimates are approximate, and are derived from discussions and information provided by the health insurance industry. They do not represent firm quotations or commitments by any plan or company to offer programs within the price ranges as shown. They are displayed only because they do illustrate for the House that the level of benefits recommended is neither overly expensive on the one hand, nor dangerously lower than the level of protection now commonly provided in employer-offered plans on the other.

As indicated in the Appendix, premium costs will vary with three factors.

1. *Geographic location:* Premium levels will reflect general differences in cost of living and medical care prices from one region to another. Accordingly, premium estimates are given for highest- and lowest-cost areas as well as for the midpoint of that range.

2. *The manner in which the cost-sharing limit is reached:* Premium costs for a plan with a given cost-sharing limit will vary depending on what combination of deductibles and coinsurance is used to reach that cost-sharing limit.

Premium costs will be lowest when the beneficiary pays the entire cost-sharing limit as an up-front deductible before plan coverage begins, and higher when the plan shares part of the cost from the beginning. Accordingly, premium estimates are also given for six different deductible/coinsurance combinations.

The Council believes that the deductible/coinsurance configuration in any given plan should be a matter for individual decision by or negotiation between employer, employees and carrier. However, it is expected that the majority of plans purchased would tend toward the low-deductible extended coinsurance approach, such as "Sample Plans" 1 and 2 in Appendix B.

Appendix B

Plan	Estimated Annual Premium; Per-Person Spending Limit						Estimated Annual Premium; Per-Family Spending Limit, Family Policy		
	Individual Policy			Family Policy			Family Policy		
	Low	Mid	High	Low	Mid	High	Low	Mid	High
Sample 1: \$100 deductible, 80/20 coinsurance for remaining \$2,200	\$524	\$773	\$1,022	\$1,435	\$1,882	\$2,340	\$1,903	\$2,917	\$3,936
Sample 2: \$300 deductible, 80/20 coinsurance for remaining \$2,000	\$504	\$699	\$958	\$1,394	\$1,705	\$2,238			
Sample 3: \$500 deductible, 80/20 coinsurance for remaining \$1,800	\$462	\$640	\$876	\$1,280	\$1,564	\$2,051			
Sample 4: \$1,000 deductible, 80/20 coinsurance for remaining \$1,300	\$404	\$559	\$764	\$1,122	\$1,370	\$1,793	\$1,459	\$2,257	\$2,988
Sample 5: \$1,500 deductible, 80/20 coinsurance for remaining \$800	\$373	\$515	\$702	\$1,036	\$1,265	\$1,653			
Sample 6: \$2,300 deductible, no coinsurance	\$344	\$503	\$662	\$787	\$1,018	\$1,260			

3. *How the cost-sharing limits are applied:* The estimated average premium cost falls a reasonable distance below the \$2,100 family and \$840 individual employer

premium contribution tax cap currently proposed by the Administration and supported by the AMA.

Eugene A. Stead, Jr., M.D.



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All Contraceptives Have Problems: Toxic-Shock Syndrome and the Vaginal Contraceptive Sponge

FOUR reported cases of toxic-shock syndrome (TSS) meeting CDC criteria occurred in late 1983 among users of the vaginal contraceptive sponge (Today*). The first patient, a Georgia resident, developed symptoms on October 16, while using a sponge for the first time. She was 37 days post-partum. The second patient, from Oregon, developed symptoms on November 14 following several unsuccessful attempts at sponge removal that resulted in fragmentation of the product. The third case occurred on November 20 in a woman from California; the sponge had been in place 32 hours and was removed with difficulty. The fourth case, also from California, occurred on December 10 in a woman who had left the sponge in place for 5 days. Patients ranged in age from 20 to 29 years; all were white, non-Hispanic. None was menstruating at the time symptoms developed.

All patients manifested fever, hypotension, diffuse rash, desquamation, nausea, vomiting, myalgias, mucous membrane hyperemia, and vaginal discharge. All were hospitalized and treated with intravenous fluids and antimicrobial agents, and all recovered. Vaginal cultures in every case were positive for *Staphylococcus aureus*.

The Today Vaginal Contraceptive Sponge was introduced to the over-the-counter market in June 1983. This sponge is made of polyurethane impregnated with the spermicide nonoxonyl-9 and is intended to provide 24 hours of contraception. The manufacturer (VLI Corporation) estimates that, as of December 1983, 5 million sponges had been used by more than 250,000 women in 24 western and southern states. During clinical trials, the average woman using only this method of contraception used 10 sponges per month. At the time the sponge was licensed, the U.S. Food and Drug Administration (FDA) required that the package insert contain a warning that clinical trials had not been large enough to assess the risk of TSS and that users should seek medical care if symptoms compatible with TSS developed. Instructions for sponge use indicate that it should not be left in place for more than 30 hours.

Following a meeting with FDA representatives on December 16, the manufacturer highlighted the warning on the package insert and placed a similar warning on the outer box.

* Use of trade names is for identification only and does not imply endorsement by the Public Health Service or the U.S. Department of Health and Human Services.

Reprinted from MMWR, Volume 33, Number 4, February 3, 1984.

Women who use contraceptive sponges should read the package insert carefully and follow the manufacturer's directions. Users who experience difficulty removing a sponge and/or sponge fragmentation should consult a physician. Women who have had TSS, particularly if it was associated with the use of a contraceptive sponge or tampon, should also consult a physician before beginning or resuming use of either. Similarly, post-partum women, who may be at increased risk of developing TSS, should seek medical advice before using the contraceptive sponge. *Reported by GA Faich, S Sobel, J Bilstad, National Center for Drugs and Biologics, U.S. Food and Drug Administration, Rockville, Maryland; Respiratory and Special Pathogens Epidemiology Br, Div of Bacterial Diseases, Center for Infectious Diseases, CDC.*

Editorial Note: This report of four TSS cases among women using the contraceptive sponge is presented to inform physicians that a potential problem may exist and to encourage the reporting of additional cases. Given the small number of known cases and the potential reporting biases, the risk of TSS associated with contraceptive-sponge use remains uncertain.

All contraception methods, as well as unprotected intercourse, involve risk either from the methods themselves or from unintended pregnancy. The contraceptive sponge is an effective means of contraception, with a failure rate similar to that for diaphragms; thus, the overall magnitude of the health risks associated with contraceptive-sponge use, including TSS, should be compared with the health risks of other methods of contraception and unprotected intercourse.

If one assumes that the four cases reported so far were all attributable to contraceptive sponges, a minimum estimate of the incidence of nonmenstrual TSS associated with sponge use would be 10 cases (95% CI Poisson distribution, 3-20) per year per 100,000 women who use contraceptive sponges as their only method of contraception. (In comparison, five to 10 menstrual cases per year are expected among 100,000 women who use tampons). Current mortality from TSS is 3%; therefore, 0.3 deaths (0.1-0.8) per year would be expected from these 10 cases of TSS among contraceptive-sponge users, in addition to an estimated 1.2 deaths related to pregnancy due to contraceptive-sponge failure. The overall number of deaths (1.5) attributable to contraceptive-sponge use would thus be comparable to the number of deaths associated with the use of other

effective contraception methods (range 0.1-5.2/100,000 women 20-29 years of age, depending on method used) and less than the risk of death from pregnancy among women using no contraception (8.3/100,000 women 20-29 years of age).

Although not included in these calculations, the use of contraception methods other than the contraceptive sponge may also affect the risk of developing TSS. For example, cases of nonmenstrual TSS among diaphragm users have been reported previously, and, to date, 18 definite and five probable cases associated with diaphragm use have been

reported to CDC. Conversely, the use of oral contraceptives may reduce the risk of developing menstrual TSS.

Physicians and other health personnel are requested to report all suspected TSS cases to their state health departments, which will forward copies of the reports to CDC. Pending revision of the TSS report form, the method of contraception in suspected cases should be included in the "other information" section of the current form. TSS report forms can be obtained from local and state health departments or directly from CDC (telephone 404-329-3687).

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Raleigh: (919) 872-1848

Wilmington: (919) 799-0655



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Bulletin Board

Continuing Medical Education

Please note: 1. The Continuing Medical Education Programs at Bowman Gray, Duke, East Carolina and UNC Schools of Medicine, Dorothea Dix, and Burroughs Wellcome Company are accredited by the American Medical Association. Therefore CME programs sponsored or cosponsored by these schools automatically qualify for AMA Category I credit toward the AMA's Physician Recognition Award, and for North Carolina Medical Society Category A credit. Where AAFP credit has been obtained, this also is indicated.

IN STATE

March 1-8

Review of Clinical Chemistry Seminar

Place: Greenville

Fee: \$315

Credit: 46 hours

Info: Mary C. Valand, Continuing Medical Education, ECU School of Medicine, Box 7224, Greenville 27834. 919/758-5200

March 6

"Duke Tuesday"

Place: Durham

Credit: 5 hours Category I AMA

Info: Linda Mace, Box 3707, Duke University Medical Center, Durham 27710. 919/684-2033

March 6-7

"The Least Restrictive Alternative: Programmatic and Management Issues"

Place: Raleigh

Info: 919/966-5463

March 7

Cardiovascular Disease Update

Place: Sanford

Credit: 6 hours Category I AMA

Info: R. S. Cline, M.D., Central Carolina Hospital, Sanford 27339. 919/774-4100, ext 394

March 7-10

"Internal Medicine: 1984"

Place: Chapel Hill

Credit: 25 hours Category I AMA

Fee: \$250.00

Info: William B. Wood, M.D., 231 MacNider Bldg 202H, UNC School of Medicine, Chapel Hill 27514. 919/962-2118

March 14

Current Concepts in Family Practice

Place: Greenville

Credit: 6.5 hours Category I AMA

Fee: \$50

Info: Mary C. Valand, Continuing Medical Education, ECU School of Medicine, Box 7224, Greenville 27834. 919/758-5200, ext 208

March 15-16

"Eighth Annual Cancer Research Symposium"

Place: Chapel Hill

Credit: 11 hours Category I AMA

Info: Mrs. Mimi Minkoff, Cancer Research Center, UNC School of Medicine, Chapel Hill 27514. 919/966-3036

March 18-21

"Improving Residency Rotations: Curriculum Planning and Negotiation"

Place: Rougemont

Credit: 20 hours Category I AMA

Info: Dr. Katharine Munning, 407 Crutchfield Street, Durham 27705. 919/471-2571

March 21

Cardiovascular Disease Update

Place: Sanford

Credit: 6 hours Category I AMA

Info: R. S. Cline, M.D., Central Carolina Hospital, Sanford 27339. 919/774-4100, ext 394

March 28-31

"Clinical Epidemiology"

Place: Chapel Hill

Credit: 24 hours

Info: Ruth De Blik, 322 MacNider Bldg, 202H, UNC School of Medicine, Chapel Hill 27514. 919/966-3641

April 8-11

"Administrative Skills: Faculty as Managers"

Place: Rougemont

Credit: 20 Hours Category I AMA

Info: Dr. Katharine Munning, 407 Crutchfield Street, Durham 27705. 919/471-2571

April 10

"37th Annual Medical Symposium: Pulmonary Medicine"

Place: Greensboro

Info: L. S. Slotnick, M.D., 1018 North Elm Street, Greensboro 27401. 919/275-7238

April 11-14

"3rd Annual Spring OB/GYN Symposium"

Place: Durham

Credit: AMA, ACOG

Info: Cindi Easterling, Box 3306, Duke University Medical Center, Durham 27710. 919/684-6485

April 12

"North Carolina Neuro-Ophthalmology Review"

Place: Chapel Hill

Credit: 2.5 hours Category I AMA

Info: Baird S. Grimson, M.D., UNC School of Medicine, Chapel Hill 27514.

April 20-21

"Carolina Ocultome Workshop"

Place: Chapel Hill

Credit: 13 hours Category I AMA

Info: David E. Eifrig, M.D., UNC School of Medicine, Chapel Hill 27514.

April 25

"Current Concepts in Otolaryngology for Primary-Care Physicians"

Place: Chapel Hill

Credit: 6 hours Category I AMA

Fee: \$50.00

Info: Harold C. Pillsbury, M.D., UNC School of Medicine, Chapel Hill 27514

April 27

"Biochemistry Symposium"

Place: Chapel Hill

Info: William B. Wood, M.D., 231 MacNider Bldg, 202H, UNC School of Medicine, Chapel Hill 27514. 919/962-2118

May 10-11

Infectious Disease Update 1984

Place: Greensboro

Fee: \$75

Credit: 11 hours Category I AMA

Info: Fred Levick, Greensboro AHEC, 1200 North Elm Street, Greensboro 27401. 919/379-4025

May 17-19

Floyd W. Denny Alumni Lecture Series

Place: Chapel Hill

Info: Gerald W. Fernald, M.D., Pediatrics, 509 Burnett-Womack Bldg, 229H, UNC School of Medicine, Chapel Hill 27514. 919/966-2085

May 18-20

Pathokinesiology of Cerebral Palsy

Place: Chapel Hill

Info: Darlene S. Slaton, Physical Therapy, C 221H, UNC School of Medicine, Chapel Hill 27514. 919/966-4708

May 25-26

13th Annual Seminar: Gut and Lung Problems in Pediatrics

Place: Durham

Credit: 12 hours

Fee: \$60

Info: Alexander Spock, M.D., Box 2994 Duke University Medical Center, Durham 27710. 919/681-3364

May 25

Pediatrics Day

Place: Greenville

Credit: 7 hours

Fee: \$55

Info: Mary C. Valand, Box 7224 ECU School of Medicine, Greenville 27834. 919/758-5200

June 1-2

Neurology for the Practicing Physician

Place: Chapel Hill

Credit: 10 hours Category 1 AMA

Info: Colin D. Hall, M.D., Neurology, UNC School of Medicine, Chapel Hill 27514. 919/966-2526

June 6-7

Fellows Symposium

Place: Chapel Hill

Info: John J. Frey, M.D., 231 MacNider Bldg 202H, Chapel Hill 27514.

June 22-23

American Heart Association, North Carolina Affiliate

35th Annual Meeting and Scientific Sessions

Place: Durham

OUT OF STATE**March 4-10**

"Sports Medicine"

Place: Snowshoe, WVA

Credit: 20 hours Category 1 AMA

Info: Cindi Easterling, Box 3306, Duke University Medical Center, Durham 27710. 919/684-6485

March 5-7

"Gold Coast Seminar: Pediatrics"

Place: West Palm Beach, FL

Credit: AMA, AAFP

Info: Continuing Medical Education, Box 3306, Duke University Medical Center, Durham 27710. 919/684-6485

March 8-11

"New Horizons for Psychosomatic Medicine"

Place: Hilton Head, SC

Credit: 20 hours Category 1 AMA

Info: Joan K. Erpf. 316/379-0191

April 9-11

"Gold Coast Seminar: OB/GYN"

Place: West Palm Beach, FL

Credit: AMA, AAFP

Info: Continuing Medical Education, Box 3306, Duke University Medical Center, Durham 27710. 919/684-6485

May 7-9

Gold Coast Seminar: Medicine

Place: West Palm Beach, FL

Credit: AMA, AAFP

Info: Continuing Medical Education, Box 3306 Duke University Medical Center, Durham 27710. 919/684-6485

May 30-June 2

AACA 1984 Spring Seminar in Anesthesiology

Place: Hilton Head, SC

Info: Program Director, American Academy of Clinical Anesthesiologists, P.O. Box 11691, Knoxville, TN 37939-1681. 615/588-6279

May 31-June 2

The Sea Level Invitational Conference on Geriatric Medicine

Place: Sea Level, GA

Info: Mary C. Valand, CME, ECU School of Medicine, Greenville 27834. 919/758-5200

June 4-8

Cornell University Diagnostic Radiology Update Emphasizing Advances in Imaging and Interventional Procedures

Place: Bermuda

Credit: 30 hours Category 1 AMA

Fee: \$400

Info: Ann Wold, Gallagher/Wold, Inc., 420 Lexington Ave., New York 10170. 212/986-1277.

June 27-30

Dermatology for Non-Dermatologists

Place: Myrtle Beach, SC

Credit: 15.5 hours Category 1 AMA

Fee: \$350

Info: A. Langen, Dermatology, Box 3135 Duke University Medical Center, Durham 27710. 919/684-6728

Letters to the Editor

Kudos

To the Editor:

I have wanted to write this letter for several months, but the only way to do things (for me) is to do them when they are on my mind.

Within the span of time that you have been editor of the *North Carolina Medical Journal*, it has become one of my favorite journals. Your choices of changes in style, format, and content, plus your personal input, have made it a pleasure to read. Thank you for this service.

W. M. Fowlkes, M.D.
1209 Glendale Drive
Raleigh 27612

To the Editor:

Our staff was very impressed with the blue pages (645-656) appearing in the October 1983 issue (volume 44, number 10) of the *North Carolina Medical Journal*. I feel it would be very valuable to be able to distribute some of these tracts to our patients. I was wondering if it would be possible for the Coastal Eye Clinic to purchase a supply of these.

Cooper Kunkel, M.D.
1411 Tatum Drive
New Bern 28560

The October issue of the Journal was a particularly successful one, and we are pleased that you have found it useful. Any reader of the Journal is free to copy and distribute articles we publish, but we have not yet considered having extra copies of the blue pages printed for distribution. You can purchase extra copies of individual issues for \$2 each.

To the Editor:

Congratulations for producing a beautiful, readable and more interesting *North Carolina Medical Journal*. I just want to tell you that I find your new format more readable, well-rounded and interesting. You are to be congratulated for your efforts. The North Carolina Medical Society is indeed fortunate to have the benefit of your enormous talents and vast experience in producing this top-flight journal.

Please keep up the good work. I look forward to reading your *Journal* now.

Bertram W. Coffey, M.D.
2800 Blue Ridge Road
Raleigh 27619

About Other Letters to the Editor:

To the Editor:

In the December 1983 issue of the *North Carolina Medical Journal* (44:770-771) there was an editorial from Dr. Robert Phillips of Greensboro which I thought was very perceptive and contributed a great deal to the editorial pages. At the end of Dr. Phillips' editorial you invited readers to express an opinion regarding a regular column of

this sort. This letter is to heartily endorse such a practice; even if the number of letters received is such that you are not able to provide one with each issue, I think it would be a very valuable forum for physician opinion.

Charles M. Hassell, M.D.
Moses H. Cone Memorial Hospital
Greensboro 27420

To the Editor:

This letter is in reference to the letter by Dr. Claude A. Frazier, M.D., about Uniform Donor Cards [NCMJ 44:827 (December 1983)].

Since 1950, almost 250,000 North Carolinians have signed donor cards from the North Carolina Eye & Human Tissue Bank, Inc. willing their eyes, any needed parts, and their bodies for anatomical study. About 8,500 pairs of eyes have been retrieved and used by ophthalmologists in North Carolina. Our affiliation with other organ procurement centers in the state has provided other tissues and vital organs.

The North Carolina Eye & Human Tissue Bank, Inc. now has two satellite programs: the Triangle Area (Duke, VA, and N.C. Memorial Hospitals) and Charlotte Memorial Hospital.

The North Carolina Eye & Human Tissue Bank, Inc. has had an exhibit every year for the past thirty-three years at the annual North Carolina Medical Society Meeting.

All of the ophthalmologists who have served and are serving on the Regional Board of Directors have done so free of charge.

In thirty-three years there has NOT been an article about the North Carolina Eye & Human Tissue Bank's activities of supplying corneal and scleral tissue to ophthalmologists for North Carolina citizens. We would appreciate an article in the *Journal* about N.C. Tissue Donation and Retrieval.

L. Byerly Holt, M.D.
3195 Maplewood Avenue
Winston-Salem 27103

The editor will poke his colleagues.

Carolina History

To the Editor:

I have thoroughly enjoyed the papers on North Carolina medical history and I have just written George Harrell a note acknowledging his beautiful commentary entitled "The Early Years at Bowman Gray." I had heard many of the important features of his pioneering work there, and his comments have placed it all in appropriate perspective. He is deserving of so much credit for such a wide array of contributions, and I simply could not be more pleased than by the fact that this was fully recognized when he received an honorary degree from Duke at Commencement.

David C. Sabiston, Jr., M.D.
Duke University Medical Center
Durham 27710

About the Blue (Yellow) Pages

To the Editor:

In talking with Marguerite Tracy recently, she made the excellent suggestion that the new "blue section" (now yellow) of the *North Carolina Medical Journal* would be an excellent medium for emphasizing and informing our physicians about the increasing importance and some of the

differences of practice in an older population — and the section might also serve as a tear-out for medical information geared, like the Harvard Medical Letter, to the layman.

It is good to have you use your experience and expertise to inject new life and new usefulness into our state *Journal*.

Monroe T. Gilmour, M.D.

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Use the *Journal* to advertise for sale or wanted items of goods or service as well as professional or community notices or ethical note. Rates: \$25 first 25 words or less for non-members, \$15 first 25 words or less for members, 25¢ each additional word, 10% discount additional issues. Write the *North Carolina Medical Journal*, P.O. Box 3910, Duke University Medical Center, Durham, NC 27710.

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References: 1. Kales A et al: *J Clin Pharmacol* 17:207-213, Apr 1977 and data on file, Hoffmann-La Roche Inc., Nutley, NJ. 2. Kales A: Data on file, Hoffmann-La Roche Inc., Nutley, NJ. 3. Zimmerman AM: *Curr Ther Res* 13:18-22, Jan 1971. 4. Kales A et al: *JAMA* 241:1692-1695, Apr 20, 1979. 5. Kales A, Scharf MB, Kales JD: *Science* 201:1039-1041, Sep 15, 1978. 6. Kales A et al: *Clin Pharmacol Ther* 19:S76-S83, May 1976. 7. Kales A, Kales JD: *Pharmacol Physicians* 4:1-6, Sep 1970. 8. Frost JD Jr, DeLucchi MR: *J Am Geriatr Soc* 27:541-546, Dec 1979. 9. Dement WC et al: *Behav Med* 5:25-31, Oct 1978. 10. Vogel GW: Data on file, Hoffmann-La Roche Inc., Nutley, NJ. 11. Karacan I, Williams RL, Smith JR: The

sleep laboratory in the investigation of sleep and sleep disturbances. Scientific exhibit at the 124th annual meeting of the American Psychiatric Association, Washington, DC, May 3-7, 1971. 12. Pollak CP, McGregor PA, Weitzman ED: The effects of flurazepam on daytime sleep after acute sleep-wake cycle reversal. Presented at the 15th annual meeting of the Association for Psychophysiological Study of Sleep, Edinburgh, Scotland, June 30-July 4, 1975. 13. Data on file, Hoffmann-La Roche Inc., Nutley, NJ.

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Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. An additive effect may occur if alcohol is consumed the day following use for nighttime sedation. This potential may exist for several days following discontinuation. Caution against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Potential impairment of performance of such activities may occur the day following ingestion. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, abrupt discontinuation should be avoided with gradual tapering of dosage for those patients on medication for a prolonged period of time. Use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in severely depressed patients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, lightheadedness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase; and paradoxical reactions, e.g., excitement, stimulation and hyperactivity.

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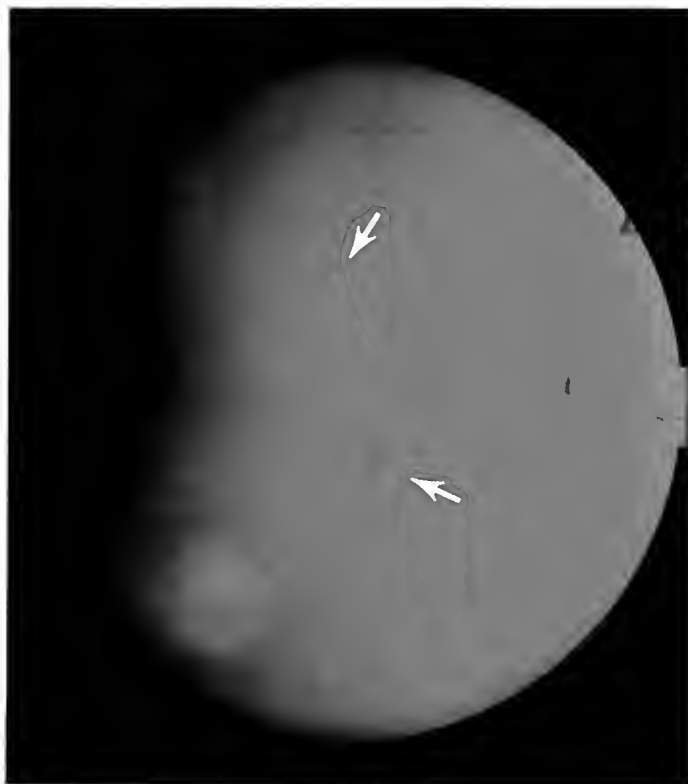
Official Journal of the NORTH CAROLINA MEDICAL SOCIETY

April 1984, Volume 45, No. 4

Sudden Vision Loss by David B. Matchar, M.D., C. Edward Coffey, M.D., and John R. Feussner, M.D.

An elderly man with pain in his calf also had sudden vision loss caused by a cholesterol embolus (right arrow) with a cotton wool spot (left arrow) and an area of retinal pallor indicating infarction

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Features for Patients

Learning Disability — page 237

by Robert J. Thompson, Jr., Ph.D.

Help for the Learning Disabled — page 242

by Margaret Sigmon and Wendy Speir

Toxic Encounters: Chloroquine — page 245

by Ronald B. Mack

1984 Annual Meeting: May 2-5,
Pinehurst

1984 Sports Symposium: June 29-July 1,
Wrightsville Beach

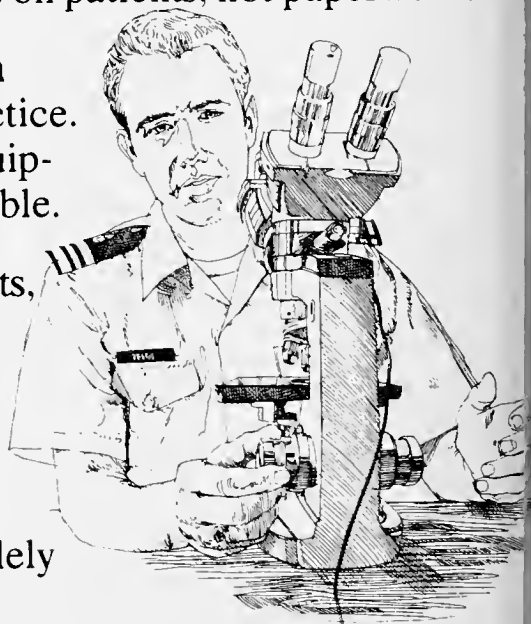
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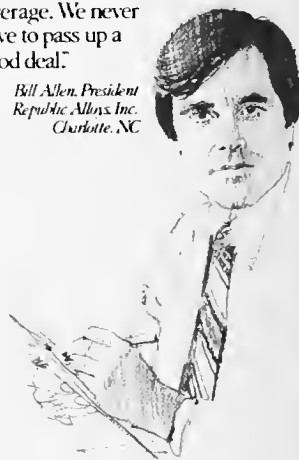
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Late Reporting of Sudden Vision Loss

David B. Matchar, M.D., C. Edward Coffey, M.D. and John R. Feussner, M.D.

SUDDEN loss or change of vision is an obvious concern for most people, yet for many elderly individuals visual defects are accepted as part of the aging process. As a result, the elderly often fail to report visual changes or represent them inaccurately.¹ In these patients, directed questioning accompanied by a methodical search for objective information on physical examination is of particular importance. In this report, we present a patient whose visual problem was identified through directed questioning; the anatomic cause of the problem was established on initial ophthalmoscopic examination performed in the clinic.

Case Report

H.J.O. is a 78-year-old man referred to the Durham VA Medical Center by his private physician for evaluation of calf pain. During triage examination he described the sudden appearance one month earlier of a dark red, green or blue spot in his lower visual field which was particularly noticeable when he looked to the left or closed his left eye. He felt well otherwise except for a 1-2 year history of right calf pain brought on after walking a few blocks and relieved by rest. He denied prior episodes of vision loss, weakness, numbness, dizziness, jaw or scalp pain, headache or dysarthria. Current medications included aspirin, 650 mg twice a day, and dipyridamole, 50 mg twice a day.

The physical examination revealed a thin, alert, elderly man. Vital signs were normal: weight 59 kg, blood pressure 130/70 mm Hg, pulse 72 beats/min, regular rate. All peripheral pulses were palpable and symmetrical including those of the distal lower extremities. He had bilateral carotid and femoral bruits and an abdominal bruit. Chest was clear to percussion and scattered rhonchi were heard throughout both lung fields. Cardiac examination was normal and no murmurs or rubs were heard. An S4 gallop was present. Extraocular movements and pupillary responses were normal. A right infero-nasal quadrant visual field loss to confrontation was noted. On ophthalmoscopic examination, no opacities were noted in cornea, lens, aqueous or vitreous. Funduscopy examination revealed an orange refractile cholesterol plaque in the supero-temporal artery of the right eye. There was a diminishing distal caliber of the vessel and a pale retina with cotton wool spots [see cover, low power photograph demonstrating cholesterol embolus (upper arrow), cotton wool spot (lower arrow), and area of retinal pallor indicating infarction]. Formal visual fields were performed, which confirmed the infero-nasal visual

defect (fig. 1). A mild refractive error was fully correctable by pin hole. The remainder of the neurologic examination demonstrated only mild generalized wasting and decreased vibration sense over both distal lower extremities. Laboratory evaluation included a normal hemogram and coagulation studies, and an EKG which showed a sinus bradycardia at a rate of 58.

Discussion

The anatomic etiology of visual loss can often be defined through basic maneuvers available to the non-ophthalmologist.^{2,3} The subsequent evaluation is directed at

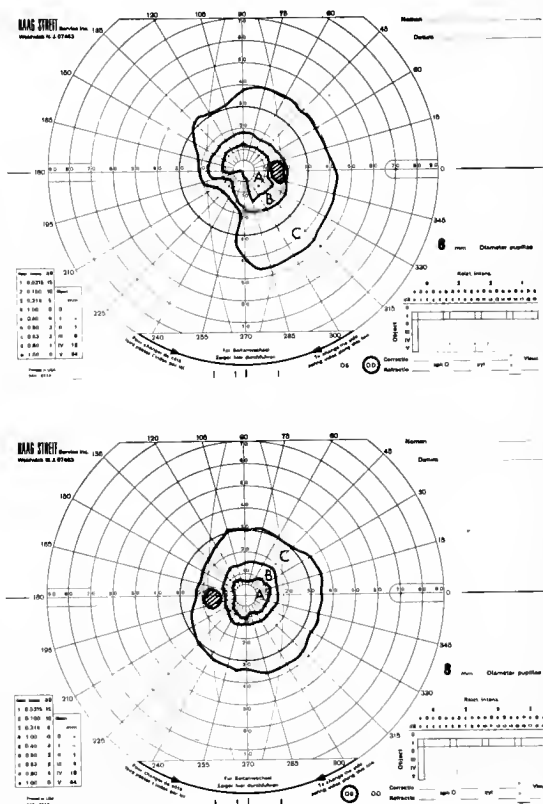


Figure 1. Formal visual fields; note prominent inferonasal field defect O.D. for all targets. Letters correspond to different colors, sizes and intensities of the targets: A = red, 3 mm, intensity 4; B = white, 1mm, intensity 3; C = white, 1 mm, intensity 4.

From the Ambulatory Care Section, Durham VA Medical Center and the Divisions of General Internal Medicine and Neurology, Duke University Medical Center, Durham 27710.

establishing the pathologic etiology so that appropriate therapy may be initiated.

Most patients with retinal infarction are presumed to have had embolization of cholesterol, fibrin or platelet aggregates from the internal carotid system to branches of the ophthalmic artery.⁴ Perhaps 5% of retinal infarctions^{4, 5} are caused by emboli from a cardiac source, for example, subacute bacterial endocarditis, myocardial infarction or valvular disease including mitral valve prolapse. Therefore, a cardiac history and physical examination, supplemented when appropriate by laboratory data (erythrocyte sedimentation rate, blood cultures, EKG, echocardiogram, Holter monitoring), are required in every patient. Other less common causes of retinal infarction include glaucoma, giant cell arteritis, polycythemia and thrombocytosis. Migraine headaches may mimic amaurosis fugax but rarely if ever cause retinal infarction.

If surgery is being strongly considered as a therapeutic alternative, angiography is the most accurate and reliable technique for defining the presence and extent of carotid atherosclerosis in patients with retinal infarction. Noninvasive procedures may have a role in the evaluation of asymptomatic or mildly symptomatic patients, but they do not obviate the need for angiography in the surgical candidate.⁶

Medical treatment of atherosclerosis is limited by our inadequate understanding of its pathogenesis. Anti-coagulation and anti-platelet agents have been employed,⁷ but only aspirin has been shown to reduce stroke in a satisfactory study.⁸

Surgical treatment is limited by the diffuse character of atherosclerosis as well as the frequency of co-morbid conditions. Removal of the apparently offending lesion or bypass would appear ideal, but data demonstrating efficacy are limited. The only randomized prospective study of extracranial arterial occlusive disease to date indicates that

surgical treatment of carotid disease surpassed medical therapy only when the disease was isolated.⁹ Unfortunately, as is the case with carotid bruit, retinal infarction is frequently a marker of extensive vascular disease, particularly coronary artery disease.¹⁰ Visible cholesterol emboli themselves bode poorly for patients with retinal infarction as they have been associated with decreased survival.¹⁰

Course

In view of the patient's age and generalized vascular disease, he was continued on aspirin and dipyridamole without further evaluation. Four months later he was seen by another ophthalmologist. At that time he had had no further neurological or visual complaints. The plaque and field cut remained unchanged. He was referred to a vascular surgeon, who performed carotid arteriography. Bilateral proximal ulcerative lesions with mild stenosis were noted. Endarterectomy was performed on the right carotid artery. There were no apparent complications and the patient was discharged on aspirin and dipyridamole.

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Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is used, potassium tablets should not be used. Hyperkalemia occurs, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K⁺ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, not K⁺ intake. Associated widened QRS complex or arrhythmias require prompt additional therapy. Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy, after weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and thiazide may appear in breast milk. If their use is essential, the mother should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. A severe exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B, corticosteroids or corticotropin [ACTH]). Periodic BUN and creatinine determinations should be made, especially in elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe carefully for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be increased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant actions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the hypotensive effect of nondepolarizing muscle relaxants such as succinylcholine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual cationic components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN, azotemia or both, hyperglycemia and glycosuria (diabetic requirements may be altered), hyperuricemia and gout, alkali intoxication (in hypokalemia), decreasing alkali reserve, possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be taken cautiously and serum potassium levels determined. Continue corrective measures and 'Dyazide' should be discontinued if values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use of chlorpromazine may increase the risk of severe hypotension. Serum FBT levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Thiazides reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, pruritus, other dermatological conditions; nausea and vomiting, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, narcotics); Necrotizing vasculitis, paresthesias, icterus, cretinism, xanthopsia and respiratory distress including pulmonary and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual cationic components. Rare instances of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supply: 'Dyazide' is supplied in bottles of 1000 capsules; 30 Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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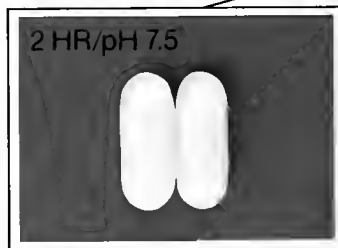
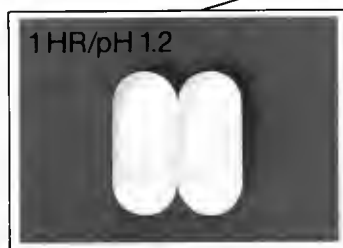


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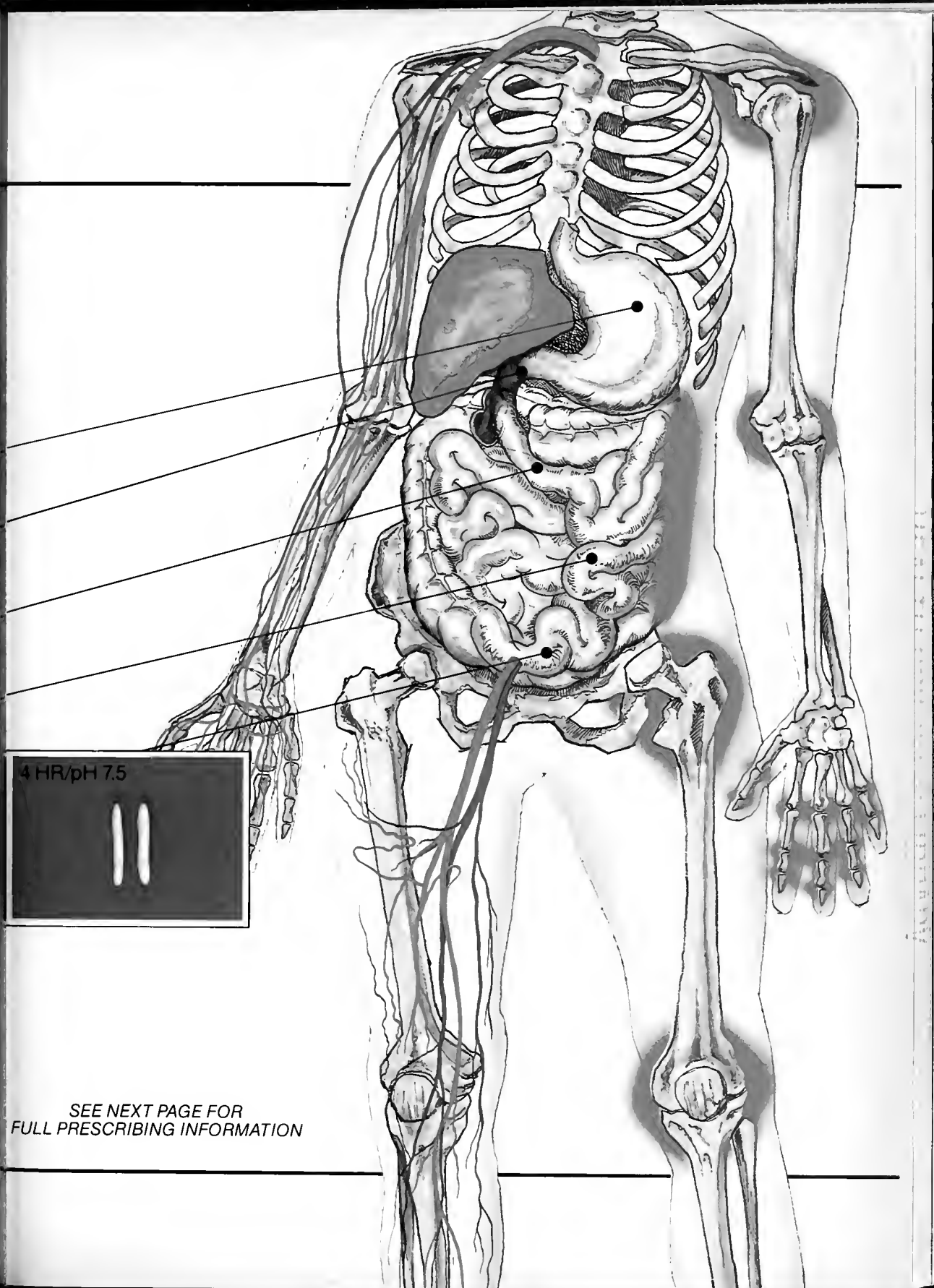
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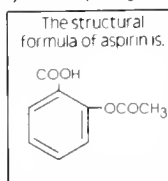
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ZORprin (ASPIRIN) Zero-Order Release

DESCRIPTION: Each capsule-shaped tablet of Zorprin contains 800 mg of aspirin, formulated in a special matrix to control the release of aspirin after ingestion. The controlled availability of aspirin provided by Zorprin approximates zero-order release, the *in vitro* release of aspirin from the tablet matrix is linear and independent of the concentration of the drug. **CLINICAL PHARMACOLOGY:** Aspirin, as contained in Zorprin, is a salicylate that has demonstrated anti-inflammatory and analgesic activity. Its mode of action as an anti-inflammatory and analgesic agent may be due to the inhibition of synthesis of prostaglandins, although its exact mode of action is not known. **Zorprin dissolution is pH-dependent.** *In vitro* studies have shown very little aspirin to be released in acidic solutions, whereas, Zorprin releases the majority of its aspirin (90%) in a zero-order mode at a neutral to alkaline pH. It is this pH dependence of Zorprin that reduces direct contact between aspirin and the gastric mucosa, resulting in a reduction of its gastrointestinal side-effect potential. **Bioavailability data for Zorprin** have confirmed that plasma levels of salicylic acid and acetylsalicylic acid can be measured 24 hours after a single oral dose. This substantiates a twice daily dose regimen. Multiple dose bioavailability studies showed similar steady-state salicylate levels for Zorprin as for conventional release aspirin using the same total daily dose. Long-term monitoring of salicylate levels showed no signs of accumulation once steady-state levels were reached (4-6 days). **Studies of *in vivo* prostaglandin levels (PGE2)** have shown Zorprin plasma levels of salicylic acid and acetylsalicylic acid to reduce PGE2 levels 14 hours after a single oral 800 mg dose while an equivalent dose of aspirin produced a reduction of PGE2 levels only through six hours. Zorprin's effect on prostaglandins other than PGE2 has not been determined. **Salicylates are excreted mainly by the kidney, and from studies in humans it appears that salicylate is excreted in the urine as free salicylic acid (10%); salicylic acid (75%); salicylic phenolic (10%); acyl glucuronides (5%); and gentisic acid (<1%).** **INDICATIONS & USAGE:** Zorprin is indicated for the treatment of rheumatoid arthritis and osteoarthritis. The safety and efficacy of Zorprin have



not been established in those rheumatoid arthritis patients who are designated by the American Rheumatism Association as Functional Class IV (incapacitated, largely or wholly bedridden, or confined to wheelchair, little or no self-care). **In patients treated with Zorprin for rheumatoid arthritis and osteoarthritis, the anti-inflammatory action of Zorprin has been shown by reduction in pain, morning stiffness and disease activity as assessed by both the investigators and patients.** **In clinical studies in patients with rheumatoid arthritis and osteoarthritis, Zorprin has been shown to be comparable to conventional release aspirin in controlling the aforementioned signs and symptoms of disease activity and to be associated with a statistically significant reduction in the milder gastrointestinal side effects (see ADVERSE REACTIONS).** Zorprin may be well tolerated in some patients who have had gastrointestinal side effects with conventional release aspirin, but these patients when treated with Zorprin should be carefully followed for signs and symptoms of gastrointestinal bleeding and ulceration. **Since there have been no controlled trials to demonstrate whether or not there is any beneficial effect or harmful interaction with the use of Zorprin in conjunction with other nonsteroidal anti-inflammatory agents (NSAIs), the combination cannot be recommended (see Drug Interactions).** **Because of its relatively long onset of action, Zorprin is not recommended for antipyresis or for short-term analgesia.** **CONTRAINDICATIONS:** Zorprin should not be used in patients known to be hypersensitive to salicylates or in individuals with the syndrome of nasal polyps, angioedema, bronchospastic reactivity to aspirin, renal or hepatic insufficiency, hypoprothrombinemia or other bleeding disorders. Zorprin is not recommended for children under 12 years of age, it is contraindicated in all children with fever accompanied by dehydration. **WARNINGS:** Zorprin should be used with caution when anticoagulants are prescribed concurrently, since aspirin may depress platelet aggregation and increase bleeding time. Large doses of salicylates may have hypoglycemic action and enhance the effect of the oral hypoglycemics, concomitant use therefore is not recommended. However, if such use is necessary, dosage of the hypoglycemic agent must be reduced. The hypoglycemic action of the salicylates may also necessitate adjustment of the insulin requirements of diabetics. **While salicylates in large doses have a uricosuric effect, smaller amounts may reduce water excretion and increase serum uric acid.** **USE IN PREGNANCY:** Aspirin may harm the fetus when administered to pregnant women. Aspirin interferes with maternal and infant hemostasis and may lengthen the duration of pregnancy and parturition. Aspirin has produced teratogenic effects and increases the incidence of stillbirths and neonatal deaths in animals. **If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.** Aspirin should not be taken during the last 3 months of pregnancy. **PRECAUTIONS:** Appropriate precautions should be taken in prescribing Zorprin for patients who are known to be sensitive to aspirin or salicylates. Particular care should be used when prescribing this medication for patients with erosive gastritis, peptic ulcer, mild diabetes or gout. As with all salicylate drugs, caution should be exercised in prescribing Zorprin for those patients with bleeding tendencies or those on anticoagulants. **In order to avoid exacerbation of disease or adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when Zorprin is made a part of the treatment program.** **Patients receiving large doses of aspirin and/or prolonged therapy may develop mild salicylate intoxication (salicylism) that may be reversed by dosage reduction.** Salicylates can produce changes in thyroid function tests. **Salicylates should be used with caution in patients with severe hepatic damage, preexisting hypoprothrombinemia, Vitamin K deficiency and in those undergoing surgery.** Since aspirin release from Zorprin is pH dependent, it may change in those conditions where the gastric pH has been increased as a result of antacids, gastric secretion inhibitors or surgical procedures. **Drugs which lower serum uric acid excretion (uricosurics) may be antagonized by the concomitant use of aspirin, particularly in doses less than 20 grams/day.** Nonsteroidal anti-inflammatory drugs may be competitively displaced from their albumin binding sites by aspirin. This effect may negate the clinical efficacy of both drugs. Also, the gastrointestinal inflammatory potential of nonsteroidal anti-inflammatory drugs may be potentiated by aspirin. The combination of alcohol and aspirin may increase the risk of gastrointestinal bleeding. **Aspirin may enhance the activity of methotrexate and increase its toxicity.** Sodium excretion produced by spironolactone may be decreased in the presence of salicylates. Concomitant administration of other anti-inflammatory drugs may increase the risk of gastrointestinal ulceration. Urinary alkalinizers decrease aspirin's effectiveness by increasing the rate of salicylate renal excretion. Phenobarbital decreases aspirin's effectiveness by enzyme induction. **Pregnancy Category D.** See WARNINGS Section. **Nursing Mothers:** Salicylates have been detected in the breast milk of nursing mothers. Because of the potential for serious adverse reactions from aspirin in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the benefit of the drug to the mother. **ADVERSE REACTIONS: Hematologic:** Aspirin interferes with hemostasis. Patients with a history of blood coagulation defects or receiving anticoagulant drugs or with severe anemia should avoid Zorprin. Aspirin used chronically may cause a persistent iron deficiency anemia. **Gastrointestinal:** Aspirin may potentiate peptic ulcer, and cause stomach distress or heartburn. Aspirin can cause an increase in occult bleeding and in some patients massive gastrointestinal bleeding. However, the greatest release of active drug from Zorprin is designed to occur in the small intestine over a period of time. This has resulted in fewer symptomatic gastrointestinal side effects. **Allergic:** Allergic and anaphylactic reactions have been noted when hypersensitive individuals have taken aspirin. Fatal anaphylactic shock, while not common, has been reported. **Respiratory:** Aspirin intolerance, manifested by exacerbations of bronchospasm and rhinitis, may occur in patients with a history of nasal polyps, asthma, or rhinitis. The mechanism of this intolerance is unknown but may be the result of aspirin-induced shunting of prostaglandin synthesis to the lipoxigenase pathway and the liberation of leukotrienes, e.g. slow-reacting substance of anaphylaxis. **Dermatologic:** Hives, rashes, and angioedema may occur, especially in patients suffering from chronic urticaria. **Central Nervous System:** Taken in overdoses, aspirin provides stimulation which may be manifested by tinnitus. Following initial stimulation, depression of the central nervous system may be noted. **Renal:** Aspirin rarely may aggravate chronic kidney disease. **Hepatic:** High doses of aspirin have been reported to produce reversible hepatic dysfunction. **OVERDOSEAGE:** Overdosage, if it occurs, would produce the usual symptoms of salicylism: tinnitus, vertigo, headache, confusion, drowsiness, sweating, hyperventilation, vomiting or diarrhea. Plasma salicylate levels in adults may range from 50 to 80 mg/dl in the mildly intoxicated patient to 110 to 160 mg/dl in the severely intoxicated patient. An arterial blood pH of 7.1 may indicate serious poisoning. The clearance of salicylates in children is much slower than adults and should receive due consideration when aspirin overdoses occur in infants, salicylate half-lives of 30 hours have been reported in infants 4-8 months old. Treatment for mild intoxication should include emptying the stomach with an emetic, or gastric lavage with 5% sodium bicarbonate. Individuals suffering from severe intoxication should, in addition, have forced diuresis by intravenous infusions of sodium bicarbonate and dextrose or sodium lactate. In extreme cases, hemodialysis or peritoneal dialysis may be required. **(A plasma salicylate level of 160 mg/dl in an adult is usually considered lethal.)** **DOSEAGE & ADMINISTRATION:** In order to achieve a zero-order release, the tablets of Zorprin should be swallowed intact. **Breaking the tablets or disrupting the structure will alter the release profile of the drug.** It is recommended that Zorprin be taken with sufficient quantities of fluids (8 oz. or more). **Adult Dosage:** For mild to moderate pain associated with rheumatoid arthritis and osteoarthritis, the recommended initial dose of Zorprin is 1600 mg (2-800 mg tablets) twice a day. Because of Zorprin's prolonged release of aspirin into the bloodstream, Zorprin tablets may be taken as a b.i.d. dose. Further adjustment of the dosage should be determined by the physician, based upon the patient's response and needs. Since it will take 4-6 days to reach steady-state levels of salicylic acid with Zorprin, it is recommended dosages be given for at least one week before further adjustment. In general, patients with rheumatoid arthritis seem to require higher doses of Zorprin than do patients with osteoarthritis. **Zorprin is not recommended for children below the age of 12.** **HOW SUPPLIED:** Zorprin Tablets 800 mg: plain, white capsule-shaped tablets. **Bottles of 100 Tablets - NDC 0524-0057-01** **Caution:** Federal law prohibits dispensing without prescription. **U.S. Patent No. 4,308,251** **Manufactured and Distributed by: BOOTS PHARMACEUTICALS, INC., Shreveport, Louisiana 71106 U.S.A.**

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A New Era in Pharmacotherapy: The Need to Understand the Principles of Therapeutic Drug Monitoring

Richard H. Drew, RPh.

RELATIONSHIPS between serum drug levels and pharmacologic activity, coupled with increasing pharmacokinetic data, have made therapeutic drug monitoring a reality. This enables the clinician to individualize and optimize pharmacologic treatment while minimizing the risk of drug-induced toxicities. Interpretation and application of serum drug level data, however, require a basic understanding of pharmacokinetic concepts and principles regarding therapeutic drug monitoring. This article presents and reviews concepts such as availability, distribution and clearance, and applies these parameters to the interpretation of serum drug level data.

Although the pharmacologic effect of a drug depends on its concentration at a target organ or cell, this relationship cannot be directly quantitated. However, a correlation between serum drug levels and pharmacologic activity (therapeutic and toxic) may exist for certain agents and could be clinically utilized if both a laboratory assay and sufficient kinetic information existed.

The increase in analytical capabilities, coupled with an explosion of information regarding the pharmacokinetics and pharmacodynamics of drugs, has made the concept of therapeutic serum drug level monitoring a reality. This allows for initiation and modification of therapy based on objective laboratory data when such information is correlated with clinical parameters. This makes it possible to individualize drug therapy, thus maximizing a therapeutic effect while minimizing the risk of side effects and/or toxicity. The interpretation of these data requires a basic understanding of pharmacokinetics. Although this may be perceived by many as the ultimate answer to optimizing all pharmacologic intervention, the applications, capabilities, and limitations of serum drug level monitoring must be put in perspective to best define its therapeutic contribution. This article is intended to discuss basic pharmacokinetic concepts and other principles essential to therapeutic serum drug level monitoring.

Principles of Pharmacokinetics — A Brief Overview

Pharmacokinetics can best be described as the quantitative study of the metabolic processes and relationships between a drug dose and its concentration in biologic

fluids.¹ This correlation is the net effect of influences from drug availability, distribution and clearance. Each of these parameters establishes the unique pharmacokinetic profile of a drug and is essential to the interpretation of serum drug level data (see figure 1).

Availability

The availability of an agent for systemic distribution is largely a function of the degree of absorption. A drug's physiochemical characteristics (such as solubility and stability) influence orally administered agents, since the drug must be in solution to be absorbed (often a rate-limiting step) and cannot be chemically broken down by gastric or other body fluids. Product formulations such as sustained-release preparations (both oral and parenteral) often take advantage of solubility properties to delay or prolong absorption, while those already in solution may enhance this rate. Also, since most drugs undergo passive diffusion, only the unionized form can be absorbed. Therefore, oral agents will be dependent on gastric and intestinal pH as well as the pKa of the agent.

Route of administration may affect both the rate and the extent of drug absorption (see figure 2). Orally administered agents usually attain peak serum levels within a few hours after administration. Intravenously administered drugs result in higher, rapid peak serum drug levels, because they are able to bypass the process of passive diffusion and are already in solution. Intramuscular and subcutaneous administration usually yields rapid but lower peak serum levels when compared with the intravenous

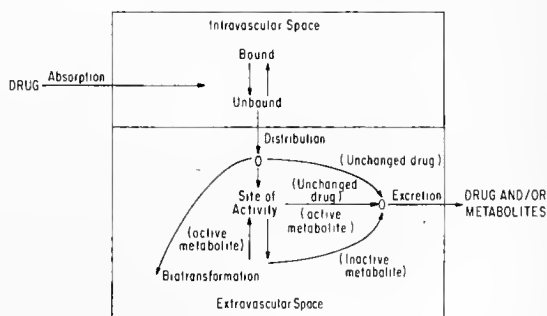


Figure 1. Drug absorption, distribution, biotransformation, and excretion.

From the Department of Pharmacy, Duke University Medical Center, Durham 27710.

Table 1
Bioavailability of Digoxin Preparations*

Product	Route of Administration	Bio-availability
Lanoxin Tablet	PO	60-80 %
Lanoxin Elixir	PO	70-85 %
Lanoxicaps	PO	90-100%
Lanoxin Injection	IM	70-85 %
Lanoxin Injection	IV	100%

* Product comparison for the Burroughs-Wellcome digoxin preparations. Substantial bioavailability differences may exist with other products.

route. However, absorption from intramuscular or subcutaneous sites may be erratic for some drugs (such as phenytoin [Dilantin] and diazepam [Valium]).^{2, 3}

It must be understood that the extent of drug absorption from a given route is not reflected by the peak serum level (as plotted on the serum concentration vs. time graph). The degree of absorption (known most commonly as bioavailability) is usually expressed as a percentage comparison between the areas under the curve (AUC) of a single dose of a drug via a given route as compared with the same dose administered intravenously (see figure 2). Bioavailability is thus not only dependent on product formulation, but also on route of administration. A good illustrative example would be the bioavailability profile of Lanoxin (see table 1).

Another factor that may influence the availability of a drug administered either orally or rectally is hepatic or gut wall metabolism following absorption, before the drug is circulated systemically. This "first-pass metabolism" may account for substantially larger requirements for oral dosing when compared with intravenous administration to produce comparable serum levels. Propranolol (Inderal)

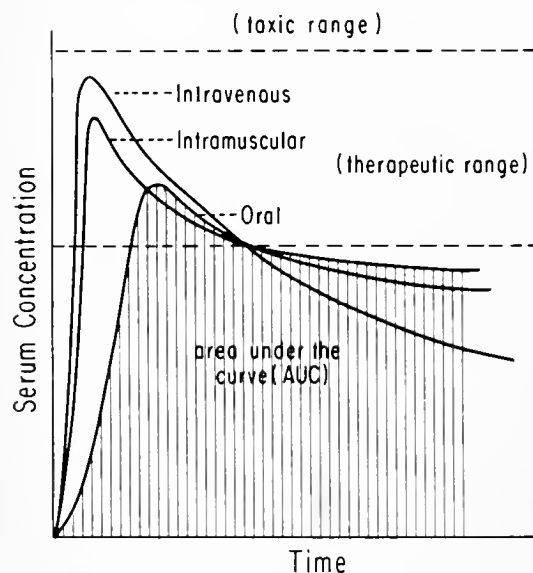


Figure 2. Absorption profile from various routes of administration.

and verapamil (Isoptin) are two examples of drugs that exhibit a high degree of first-pass metabolism.^{4, 5}

The knowledge of a drug's absorption and availability is essential in predicting the time of peak plasma levels or for interpreting laboratory results as either peak, trough or an intermediate value. Factors that influence availability (such as formulation, route of administration, etc.) must be known for the drug and may often be identified by serum drug level monitoring as the cause of a subtherapeutic or toxic response. This information is also essential in modification of a dose when a preparation or route of administration is altered during therapy.

Distribution

Following absorption, the drug undergoes distribution from the intravascular space to various extravascular tissues and fluids (see figure 1). This distribution is best

ABSORPTION

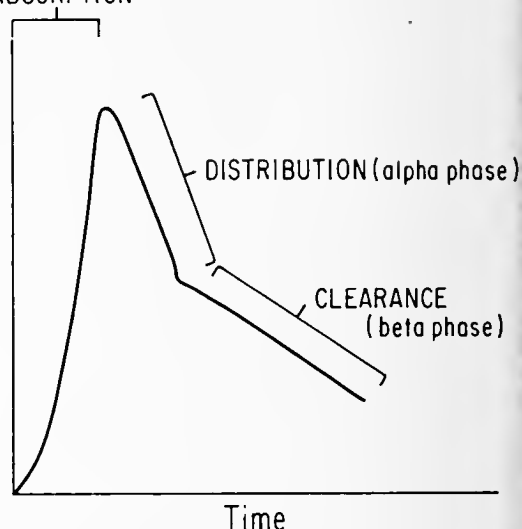


Figure 3. Illustration of drug absorption, distribution, and clearance following a single oral dose.

illustrated graphically as the early portion of the declining serum concentration vs. time curve (known as the alpha phase) (see figure 3). If simplified, the body can be pictured as a single compartment for this distribution. A relationship can be established between available drug and the serum levels resulting from its administration. This relationship, known as the volume of distribution, represents a hypothetical volume in which the drug would be distributed throughout to produce a given serum concentration. Expressed in unit volume per unit of weight (L/kg), the volume of distribution does not truly represent a real body space, but rather provides a proportionality constant relating plasma concentrations to total body stores of a drug. Unfortunately, many drugs exhibit "multi-compartment" kinetics which demonstrate different rates of equilibrium.

Binding of a drug to serum proteins will also influence drug distribution. Since drugs bound to serum proteins

(primarily albumin and alpha-1-acid glycoprotein) probably cannot cross membranes, evidence exists that an equilibrium is established between bound and unbound ("free") drug, and that only this free drug possesses pharmacologic activity. Such binding may therefore vary with the level of plasma proteins. Also, other agents which may compete and thus displace drugs from protein binding sites may result in increases in free (active) drug plasma concentrations. This becomes most significant with drugs that are highly protein bound, since small changes in the bound fraction may result in large alterations in the fraction that is free (see table 2).

The concept of drug distribution and its relationship to serum drug levels is important to understand for several reasons. First of all, blood samples taken while a drug is undergoing distribution may not accurately reflect extravascular tissue or fluid levels if an equilibrium has not been established between these spaces. Therefore, concentrations at the site of activity may be increasing in the face of declining serum levels. Drugs that exhibit multi-compartment kinetics cannot be monitored by single serum drug level determinations, since this equilibrium is difficult to predict. Factors that alter plasma proteins or drug binding may influence response without necessarily changing plasma drug levels. This leads us to discuss the fact that laboratory data generated represent total (free and protein-bound) levels, and may not accurately reflect the amount of pharmacologically active (free) drug concentration. It has been postulated that similar therapeutic or toxic responses between patients at differing serum plasma concentrations of drug may be due (in part) to similar free drug concentrations. Capabilities are being developed for many drugs to measure this active fraction and may eventually lead to redefining therapeutic ranges.

Clearance

The clearance of a drug following the absorptive process is the net result of both biotransformation (metabolism) and elimination, and is responsible for determining the agent's duration of activity. It can also be illustrated graphically on the serum concentration vs. time graph and is known as the beta-phase (see figure 2).

Biotransformation of a drug may terminate its activity or lead to the formation of active metabolites, which may then undergo further metabolism or be excreted (see figure 1). Therefore, the terms "detoxify" and "inactivate" are misnomers. This transformation is due primarily to hepatic metabolism by microsomal enzyme systems to a more

water-soluble molecule for excretion and may be influenced by factors altering these enzymes or by affecting hepatic blood flow. Although many agents will be metabolized as a constant percentage of the absorbed drug (first-order kinetics), other drugs will saturate hepatic or other enzyme systems and result in a constant rate of metabolism despite total body levels (zero-order kinetics). Some agents, such as salicylates, may exhibit both first-order and zero-order kinetics, depending on the dose administered. Therefore, changes in the amount of drug administered may produce disproportionate alterations in corresponding plasma levels.

Renal excretion is the primary method of elimination for most drugs and is the net result of glomerular filtration and/or tubular secretion. The parent compound and/or its metabolites (active and inactive) may be excreted in this manner. Other minor routes of elimination may be through sweat glands, lungs, or biliary tract and may become more significant if the principal route is impaired.

Total body clearance of a drug, therefore, is the sum of both metabolism and elimination and represents the rate of drug removal from the body. This rate may also be reflected in the elimination half-life, or the time required for the serum concentration to decline by 50%. Determination of this value may assist in designing the optimum dosing schedule and predicting fluctuations in drug plasma concentrations within a dosing interval.

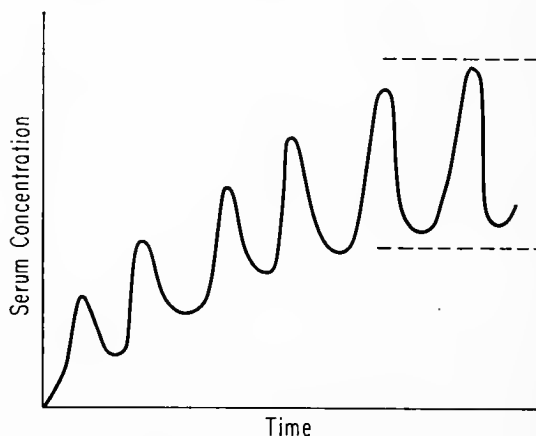


Figure 4. Establishment of steady state concentrations following repeated dosing.

Table 2
Effect of a 2% Decrease in Protein Binding of Drugs

	Before		After		% Change in Free (Active) Drug
	Fraction Bound	Fraction Free	Fraction Bound	Fraction Free	
Drug A*	98%	2%	96%	4%	100%
Drug B†	60%	40%	58%	42%	5%

* Drug A represents a highly protein-bound drug

† Drug B represents a moderately protein-bound drug

As the drug is absorbed and continues to distribute into extravascular spaces, fluctuations are seen in both peak and trough concentrations until an equilibrium is reached between administration and elimination. This equilibrium, or steady state, is usually reached after the fifth dose if the interval is close to the drug's elimination half-life (see figure 4).

The knowledge of a drug's clearance is imperative to therapeutic serum drug level monitoring. Although assays will routinely detect parent drug concentrations, the amount or accumulation of pharmacologically active metabolites may become significant in chronic dosing or if elimination is impaired. Routes of metabolism and/or excretion may be influenced by a variety of factors, and should be considered when laboratory data are interpreted. Also, knowledge of a drug's elimination half-life will assist in predicting time to achieve steady state concentrations, since peak and trough levels determined before this equilibrium is reached will be subject to fluctuations. Caution must be used, however, in extrapolating elimination half-life to predicting duration of pharmacologic effect, since many drugs continue to demonstrate activity despite "subtherapeutic levels."

Serum Drug Level Monitoring

Indications

In order for serum drug level monitoring to be effectively utilized, there are several requirements. First of all, a method to assay the compound should be developed and available for clinical use. Sufficient data must then be collected to establish and document a correlation between a pharmacologic effect and serum concentrations. Once these are available the value of serum drug level monitoring must be assessed for its contribution to patient care. Its use should be limited to situations in which more direct measurements of either efficacy or toxicity are not available; examples include the monitoring of blood coagulation studies (rather than drug plasma levels) to control therapy with the anticoagulant drugs heparin and warfarin.

Given this well defined relationship of activity to serum drug concentration, therapeutic drug monitoring can provide invaluable information in a wide variety of clinical situations. Because many agents lack objective criteria to measure pharmacologic effect or predict toxicity, the use of serum drug level monitoring can help to establish therapeutic drug concentrations more rapidly to prevent periods of inadequate control or toxicity. This is especially true if the drug is to be administered prophylactically.

Compounds that demonstrate poor relationships between the dose administered and the resulting serum concentrations can best be monitored using serum drug concentrations. This situation may result from wide pharmacokinetic differences between patients. Agents with a narrow therapeutic index (i.e., small differences between therapeutic and toxic blood levels) or those for which the implications of a subtherapeutic response would be severe are often monitored to confirm a therapeutic serum level. Noncompliance may also be documented using laboratory analysis.

Sample Collection and Laboratory Analysis

The correct timing for collection of a sample in relation

Table 3
Timing of Sample Collection for Drug Assay*

Desired Information	Time of Collection
Peak levels	Estimated point of maximum absorption
Trough levels	Prior to the next dose
Document drug toxicity	Peak level supplemented or replaced by spot level at the time of clinical toxicity
Document subtherapeutic response	Trough level supplemented or replaced by spot level at the time of subtherapeutic response
Therapeutic confirmation	Steady state trough levels may be supplemented by steady state peak levels if the drug has a short half life
Document noncompliance	Spot level

* Best accomplished following absorption and distribution phases after steady state has been reached

to the administration of a dose is essential, since the appropriate interpretation and application of the data are dependent on it. Ideally, the absorption and distribution phases should be complete and steady state should be reached before a sample is obtained. The correct timing in relation to the dose is therefore dependent on the product formulation, route of administration, and pharmacokinetic parameters of the drug (as discussed earlier). Timing is also dependent on the data desired (see table 3). Peak levels are obtained at a period estimated to result in maximum blood levels based on product formulation, route of administration, and absorptive characteristics. Trough levels are usually drawn just prior to administration of the next dose. Routine serum level monitoring done to document therapeutic levels is best done after steady state has been reached and should include a trough concentration if the drug has a short half-life. If a toxic or subtherapeutic response is clinically suspected, peak and trough levels should be supplemented with or replaced by "spot" levels at the time of the response. Documentation of noncompliance is usually done as a spot level, since most of these patients are ambulatory, thus making selection of an optimal sampling time impractical.

After the timing of the sample is determined and documented, it must be properly collected and stored for transportation to the clinical laboratory for analysis. The appropriate container must be selected to minimize interference with the assay and should be labeled with the appropriate patient data (name, room number, etc.). Also, the site of sampling is important. Collection from indwelling catheters containing heparin or those used for administering medication should be avoided. Selection of sites for venipuncture is dependent on the availability of venous access, but those done close to the site of drug administration may result in levels that are elevated because the drug has not been allowed to be diluted and distributed into the serum. The volume, type (serum or plasma) and storage of the collected sample depend on the type of assay to be utilized.

After the appropriate sample has been collected and transported to the laboratory, analysis using one of the variety of procedures may then be performed. Factors such

Table 4
Factors Affecting Serum Drug Concentrations and Their Interpretation

Drug characteristics	Patient characteristics
physiochemical properties	age
product formulation	sex
pharmacology/	pregnancy
pharmacokinetics	genetic factors
Disease state(s)	organ function (hepatic, renal, etc.)
	body composition
Concomitant drug and	Sampling and assay
food intake	timing of sample
Drug therapy	sensitivity & specificity
route of administration	of assay
compliance	
duration of treatment	

as sensitivity and specificity of the assay must be considered, as well as the turn-around time to obtain results. The laboratory must also know what must be measured, since active metabolites may be measured depending on their concentration, degree of activity, and potential for accumulation.

Interpretation of Results

Interpretation of the results of serum drug level assays requires the integration of knowledge of a drug's pharmacokinetic profile and its influences with the clinical status and response of the patient. These data should first be correlated with the collection time of the sample in relation to the dose and duration of treatment to determine whether this value represents a peak, trough, or intermediate concentration and if a steady state has been reached. Many factors may influence drug serum concentrations and their interpretation, and must be considered before continuation or modification of drug therapy is done based on this information (see table 4).

The therapeutic range of a drug may be defined as a range of serum drug concentrations associated with high degree of efficacy and a low risk of dose-related toxicity.⁷ Because

this is based on data from the general population and could not be controlled for the variety of factors that may influence patient response, it is imperative that these data be correlated with clinical status to interpret the results. Patients may therefore respond to "subtherapeutic" levels or require "toxic" concentrations (based on this established therapeutic range) for adequate response.

Conclusion

The capabilities and applications of serum drug level monitoring are now beginning to be recognized. Because of the great impact of drug therapy on patient care, interest and knowledge regarding pharmacokinetics have skyrocketed, making individualized drug therapy a reality through integration of pharmacokinetics, clinical therapeutics, and analytical sciences. However, it is only with a general knowledge of basic principles of therapeutic drug monitoring that these capabilities can be applied and maximized. Therefore, the contribution of serum drug level monitoring is largely dependent on its appropriate use.

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Pulmonary Echinococcosis: The Geographic History Scores Again

Doris S. Kelsey, M.D. and Louis deS. Shaffner, M.D.

THIS is the story of a patient with a disease rarely seen in North Carolina. The patient was a 14-year-old white girl who was admitted to the North Carolina Baptist Hospital in Winston-Salem with a 4-week history of intermittent fever, fatigue, cough, and a five-pound weight loss. A roentgenogram of the chest obtained two weeks earlier revealed a well-defined lobulated density in the left lower lung field. Subsequently a one-week course of oral tetracycline and then five days of oral erythromycin resulted in no change in clinical or radiographic findings. The patient had been in Iran from 1976 to 1978 with her father who was on military assignment.

Oral temperature was 102° F, blood pressure 112/74, pulse 92 per minute, and respirations 20 per minute. There were no abnormalities detected on physical examination. The radiographic findings and environmental history suggested the possibility of echinococcus.

The hematocrit reading was 32 volumes percent, white blood count was 13,600 cells per cu ml with a differential count of 77 neutrophils, 14 lymphocytes, 7 monocytes, 1 eosinophil and 1 basophil. Total serum protein was 7.0 grams per decaliter with an albumin/globulin ratio of 3.1/3.9. Serum submitted to the Centers for Disease Control in Atlanta, Georgia for indirect hemagglutination to echinococcus revealed a titer of 1:512.

Radiologic procedures included sonic studies of the abdomen and computerized tomography of the head and revealed no additional cysts.

The preoperative diagnosis of hydatid cyst was confirmed at surgery. A basilar segmental resection of the left lower lobe with removal of the cystic mass was performed. Pathologic report revealed the presence of hooklets within the lesion. The cystic cavity was 4 cm in diameter with several smaller cystic lesions that did not communicate with the larger one. Bacterial culture of the surgical specimen grew non-typable *Hemophilus influenzae*. This secondary infection probably explained the febrile course.

Postoperatively, the patient received intravenous cephalirin sodium for three days and then oral cephalixin for a total of seven days. The patient was discharged on the seventh postoperative day and has remained symptom-free in the year since surgery.

Discussion

Echinococcosis (hydatid cyst) is a parasitic disease

caused by infection with the larvae of *Echinococcus granulosus*, the dog tapeworm. The disease is endemic in many parts of the world with the greatest prevalence reported in Australia, South America, South Africa, the Soviet Union, and the Mediterranean. Most cases diagnosed in the United States are acquired in other countries although autochthonous cases have occurred.¹ Three cases of pulmonary echinococcosis in children from Arizona and New Mexico have been reported.²

Man is an inadvertent host of the disease usually infected by dogs that excrete the eggs in the feces. Dogs acquire the disease from ingestion of infected sheep or other intermediate hosts. Once the eggs are ingested by man, the larvae hatch in the intestine and are disseminated via hematogenous or lymphatic routes with production of hydatid cysts. The spread is via the duodenum into the portal system with the majority of cysts found in the right lobe of the liver.³ In children, however, the lung is reported to be more frequently involved than the liver. The right lung is infected more often than the left; likewise, the lower lobes are more frequently involved than the upper ones.^{4,5} Although the majority of hydatid cysts occur in the liver or lungs, they may occur in any organ or in multiple sites. The cyst is estimated to grow about 1-2 cm per year. The latent period from infection to clinical symptomatology may be quite variable depending on the site of involvement. It may be especially prolonged in the liver where a large mass may not produce symptoms. At the extreme, an interval of 50 years from infection to clinical diagnosis has been reported.³ The clinical symptoms associated with pulmonary hydatid cyst frequently include cough, hemoptysis, or chest pain. Some children may have pruritis. Roentgenographic evaluation, particularly ultrasound studies, is helpful in delineating the cystic nature of the lesion or multiple cysts. Long-standing lesions may be calcified. The most helpful laboratory test is the indirect hemagglutination test for echinococcus which is positive in about 85% of patients with liver cysts and 40% of patients with pulmonary echinococcosis. Eosinophilia is not typical.¹

The differential diagnosis of lung cysts includes bronchogenic cysts, hamartomas, granulomatous lesions, and post-inflammatory tumors of the lung.

As in this case, a presumptive diagnosis of hydatid cyst can be made based on the environmental history, radiographic studies, and serologic findings. Definitive treatment is by surgical excision of the infected cyst or preliminary sterilization of the cyst contents with a scolicedal solution prior to evacuation by surgical aspiration.

From the Departments of Pediatrics and Surgery, Bowman Gray School of Medicine, Winston-Salem 27103.

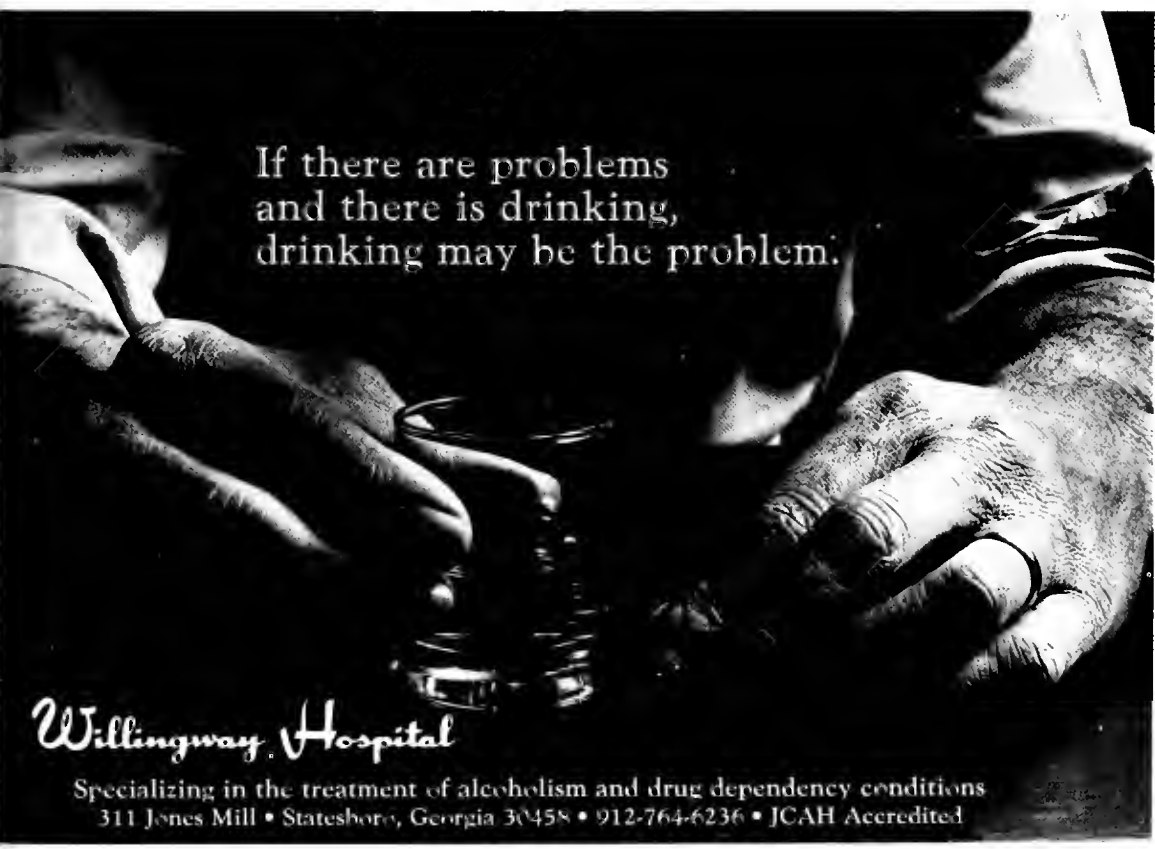
Cryosurgery has been successfully used in preventing rupture of the cyst during operation.⁶ Special care must be taken to avoid spillage of the cyst contents during surgery, as this complication has been associated with anaphylactoid reactions and metastatic dissemination. Surgical techniques to reduce complications and recurrences have been described elsewhere.⁴⁻⁶ Mebendazole⁷ has been utilized for treatment of echinococcosis in patients with inoperable or advanced disease with encouraging results. Other investigational drugs in the treatment of this disease process include praziquantel⁸ and albendazole.⁹

Acknowledgment

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If there are problems
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The Role of the Argon Laser in Plastic Surgery

Ronald Riefkohl, M.D.

LASER is an acronym for *Light Amplification by Stimulated Emission of Radiation*. This radiation is non-ionizing and therefore non-carcinogenic.

The argon laser is an optical resonator filled with argon gas, and has a 100% reflective mirror at one end and a 95% reflective mirror at the opposite end. When a high voltage is applied across the resonator, the outer orbiting electrons of argon atoms are temporarily raised to higher energy levels. As the electrons drop back to the normal energy level, a photon of light of a specific wavelength and color is emitted. As this photon bounces back and forth between the two mirrors, it strikes another excited argon atom and stimulates the emission of a second photon of the identical wavelength and color. This process continues repeatedly, stimulating more excited atoms to emit photons cooperatively before they have time to do so spontaneously and independently. This amplification process results in a beam of intense, monochromatic, coherent, directional radiation, i.e., argon laser light, that is emitted through the partially reflective mirror and transmitted through fiberoptic cables to a handpiece used to aim the laser beam at the target tissue.¹

Argon lasers produce visible blue/green light (488-514 nm) which is transmitted through clear aqueous tissues, but absorbed by pigments, particularly pigments of the complementary red color, such as hemoglobin. Cutaneous laser absorption by hemoglobin causes heat generation and coagulation of small vessels and adjacent tissue, resulting in vasocoagulation and a superficial second degree burn, which when healed will be a lighter color shade. Unfortunately, the argon lasers currently available penetrate skin to a depth of only 1.5 mm and will not coagulate vessels larger than 0.5 mm in diameter. Late histopathological skin changes are maximum at a depth of 0.1-0.4 mm, with compaction of dermal collagen, obliteration of a substantial number of dermal capillaries, and blunting of the rete ridges with epidermal atrophy as is seen after any cutaneous thermal injury.²

We have used a Cooper Medical Model 770, 5-watt argon laser (Cooper Medical, 88 Hamilton Ave., Stamford, Connecticut 06904) to treat 135 lesions. The beam was delivered through either a 1 mm or a 2 mm hand-held fiberoptic stylus. All patients with portwine stains first underwent a test spot treatment, during which a small area was treated to enable the patient to see the degree of improvement before submitting to extensive treatment as well as to eliminate any patient with a tendency to develop hypertrophic scarring. Treatment was not resumed for at least three months. Larger portwine stains were treated

sectionally because of the substantial edema that occurs and to minimize potential difficulties with wound healing.

Patients with other vascular lesions or decorative tattoos ordinarily did not undergo a test spot treatment.

Treatment was done on an outpatient basis and under local anesthesia by infiltration of 1% xylocaine. For vascular lesions, the lowest power setting that will convert the red discoloration to a whitish-grey hue was selected. This is usually in the range of 0.8-1.2 watts, with an exposure time per area of 0.2 sec. For tattoos, the object is to achieve a deep dermal burn; therefore power settings of 2.6-3 watts with exposure time of 1-5 sec are necessary. After treatment, 1% silver sulfadiazine cream was applied to the burn wound until it healed. Treated vascular lesions ordinarily healed by 14 days, but most treated tattoos did not re-epithelialize for at least four weeks.

Table 1 summarizes the cutaneous lesions treated during the previous 18 months. Many of the patients with large portwine stains have not completed treatment and those patients treated during the past three months have received only a test spot.

The portwine stain is optimally treated with the argon laser, as no other treatment modality is as effective, particularly for larger lesions. Most portwine stains fortunately are in the papillary layer of the dermis, and are thus amenable to photocoagulation. The degree of color change is quite variable, but approximately 70% of patients will be benefited. Small superficial portwine stains located on the face are nearly 100% obliterated. The best results have occurred in patients with facial portwine stains that are dark red or light purple. Other favorable attributes include a superficial location, a fair complexion, and sluggish blanching and capillary refilling of the lesion. The results with portwine stains located on the trunk and extremities have been disappointing because of minimal color change and scarring. Telangiectatic vessels and spider nevi located

Table 1
Cutaneous Lesions Treated with Argon Laser

Lesion	Number
Portwine stain	76
Capillary-cavernous hemangioma	2
Decorative tattoo	22
Traumatic tattoo	2
Facial telangiectasia	21
Spider nevus	7
Post-rhinoplasty erythema	1
Acne rosacea	3
Angiokeratoma	1
Total	135

From the Division of Plastic Surgery, Duke University Medical Center, Durham 27710.

on the face achieved nearly 100% obliteration.

Two small capillary-cavernous hemangiomas located on mucous membranes have diminished after treatment, but these lesions are expected to ultimately expand to their original size. No cutaneous capillary-cavernous hemangiomas have been treated.

Acne rosacea and post-rhinoplasty cutaneous erythema have both been treated successfully.

Superficial telangiectatic vessels located on the lower extremities have been photocoagulated unsuccessfully, in that initially there is complete obliteration, but after 8-10 weeks the vessels recanalize, probably because of their larger size.

Pigment removal from decorative tattoos has been approximately 95% complete; most patients had a few remaining speckles of pigment within a smooth atrophic scar. Traumatic tattoos have not responded to treatment, but experience has been limited to two patients.

The incidence of hypertrophic scarring with tattoos has been about 25%, and with facial portwine stains and other vascular lesions about 5%. Almost all the facial hypertrophic scars were located on the lips, chin, lateral nose, and nasolabial region. Several facial hypertrophic scars were successfully treated with repeated steroid injections. About 10% of the portwine stains on the extremities or trunk developed hypertrophic scars. There have been no other complications to date.

Recently, strawberry hemangiomas in infants have been treated with the purpose of precipitating involution but they are not obliterated by the laser itself.⁵

Patients under 12 years of age may have prolonged redness of the treated skin and are at a greater risk for hypertrophic scarring. Characteristically, portwine stains darken and thicken with aging and many also develop surface irregularities and "bubbling." Though significant lightening and smoothening will be anticipated in this age group, the color change is not as dramatic as in young adults.

Superficial capillary-cavernous hemangiomas confined to the skin may be benefited initially, but usually deeper components of the lesion may result in recanalization and recurrence. Since the argon laser will not penetrate intact skin, subcutaneous hemangiomas are not affected.

The other group of successfully treated cutaneous lesions includes facial telangiectatic vessels, spider nevi, acne rosacea, and post-rhinoplasty erythema. The vascular pathology in all of these lesions is superficially located and may be obliterated by laser photocoagulation. Due to the

small size of the lesions and consequent minimal thermal damage, the risk of hypertrophic scarring is remote.

Decorative tattoos may be removed because there is non-specific absorption of argon light by metallic-oxide tattoo pigments. Rather than vasocoagulation though, the superficial skin is vaporized by the laser beam, so that the extent of thermal injury to the deep dermis is substantially greater than for a vascular lesion and the healing time is consequently prolonged. This accounts for the much higher incidence of hypertrophic scarring with commercial tattoos. Under the best conditions a depigmented and atrophic scar with a few speckles of tattoo pigment remains. These remaining tattoo speckles have been resistant to repeat laser treatment. Either the pigment in these areas is located at a deeper level of the skin, or it has become trapped within scar tissue during healing. Also, the silhouette of a tattoo will remain evident, so for obvious outlines such as letters, the surrounding skin should also be treated to disguise the nature of the original tattoo.

Curiously, traumatic tattoos have responded poorly, perhaps because of the associated scar tissue with the entrapped debris, or the foreign debris may be too deep in the skin.

Small vascular lesions or tattoos that are appropriately situated may be more easily managed by surgical excision, since the postoperative management is easier and the results are more predictable. Other situations that may preclude the application of the argon laser include patients with a dark complexion, since there is absorption of the beam by melanin and consequently less vasocoagulation and subsequent color change. There is also the theoretical risk that should significant obliteration of a vascular lesion occur, late skin depigmentation may be just as noticeable and distressing to the patient as the original vascular lesion.

Patients with a hypertrophic scar tendency probably should not be treated. Also, vascular lesions located on the trunk and lower extremity, particularly below the knees, are unlikely to change color sufficiently to justify the increased risk for hypertrophic scarring as well as the inconvenience and expense of the treatment.

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Gastric Bariatric Surgery at North Carolina Memorial Hospital: Factors Essential for Good Results

Charles A. Herbst, Jr., M.D. and Joseph A. Buckwalter, M.D.

IN 1975 a randomized clinical trial at North Carolina Memorial Hospital determined that gastric bypass (a gastric bariatric procedure) was as effective as and produced fewer complications than the jejuno-ileal bypass.^{1, 2} On the basis of this experience we have in the last eight years used gastric bariatric operations in the treatment of morbid obesity. One of five operative procedures have been done on 575 patients.^{3, 4} Patients receiving concomitant jejuno-ileal bypass takedown and those operated elsewhere who were referred because of complications are not included. Sex, age, ideal weight, real weight, and excess weight of all five groups were comparable.

Group 1, treated by gastric bypass Roux-en-y (GB-RY), was composed of 184 patients. Table 1 lists 58 complications in 41 GB-RY patients (22%). Splenic injury (6 patients) and anastomotic leak (6 patients) carried a high incidence of morbidity, usually associated with development of a subphrenic abscess (11 patients). The six patients who had staple separation were all in the group of 31 who received a single TA-90 cartridge application and led to our adoption of a double application or suture-reinforced staple line. There were nine patients who had stomal obstruction. Four responded well to medical management and did not require surgery. Five required revisional surgery. Two patients developed marginal ulcers. One required surgery to excise the ulcer and reduce the size of the pouch which was too large. The other patient responded well to cimetidine and has had no trouble since. There was one surgically related death.

Group 2 was composed of 69 patients who had a gastric bypass loop gastroenterostomy (GB-loop). This procedure also produced a high incidence of technical complications including splenectomy (2 patients), anastomotic leak (2 patients), abscess (4 patients), and staple line separation (2 patients). There was one surgically related death.

In groups 1 and 2 the pouch, although not measured, was estimated to be between 50 and 60 ml. The stoma was 1.0-1.2 cm in diameter by measurement over a calibrated tube. The stomach was transected in the first 12 GB-RY patients and 9 GB-loop patients. Following Alden's report in 1977, describing the use of stapling instruments,⁵ we adopted a single application of the TA-90 stapler to parti-

tion the stomach in 31 GB-RY patients. Later, a double application of the TA-90 or a single TA-90 application reinforced with a nonabsorbable suture was used.

Group 3 contained 40 patients who had a greater curvature gastroplasty (GP). In these patients, the stoma was created by removing staples at the greater curvature end of the TA-90 stapling instrument. In eight patients, no staples were removed, but a C-clamp was used as described by Gomez.⁶ A double application of the TA-90 was used and the pouch was estimated to be between 40 and 50 ml. The stoma was reinforced with an inverting running Lembert nonabsorbable suture over a 10 mm bougie.

A major problem was stomal obstruction in 7 patients (table 1). For this reason we abandoned greater curvature gastroplasty. Four patients had functional obstruction in the presence of an adequate stoma demonstrable by barium and endoscopic studies. The factors responsible for stomal obstruction include edema, reduced blood supply, and crushing the area between the jaws of the stapling instrument. There were no deaths in this group.

Group 4 contained 223 patients who had a gastrogastrostomy (GG) anterior to a double-applied TA-90 staple line. Originally, the pouch was 40-50 ml but later it was made 20-25 ml by a less transverse and more oblique placement of the staples. This change allowed substitution of the TA-55 for the TA-90. The stoma, originally 1.0 cm in diameter, was also made 0.8 cm in diameter enclosed circumferentially with an absorbable running inner layer. Staples made the outer posterior layer, and a nonabsorbable running Lembert suture made the anterior outer layer. This procedure caused fewer technical complications and those that occurred were less serious than in groups 1, 2, and 3. Eleven patients developed phytobezoars requiring endoscopic removal or enzymatic digestion. Having a bezoar in fact proved to be a valuable learning experience since no patient developed a second bezoar. There was one surgically related death.

Group 5 was composed of 49 patients having a vertical banded gastroplasty (VBG). Three patients (6%) experienced surgically related complications (table 1). A window is made through both walls of the stomach just above the crow's foot and along the lesser curvature. A double application of the TA-55 staple up to the angle of His through this window creates a 20-25 ml pouch. A 1.5 x 7.0 cm polypropylene mesh collar is sutured to itself around the

From the Department of Surgery, University of North Carolina. Chapel Hill 27514.

TABLE 1
Complications in 575 Morbid Obesity Operations

	GB-RY	GB-Loop	GP	GG	VBG
Splenectomy	6	2	0	0	0
Leak	6	2	1	3	1
Abscess	11	4	0	2	0
Staple separation	6	2	1	2	0
Obstruction	9	0	7	5	0
Bezoar	0	1	1	11	0
Afferent loop	0	2	0	0	0
Reflex	0	2	0	0	0
Marginal ulcer	2	0	0	0	0
Death	1	1	0	1	0
Miscellaneous	17	15	2	23	3
Percent patients	22%	32%	28%	19%	8%

stoma to provide an outlet circumference between 5.0 and 5.5 cm.

There was good weight reduction in groups 1, 2, and 3 but the morbidity was high (table 2). The weight loss was less satisfactory in group 4 but complications were less frequent. In group 5 the weight loss appears promising and the complications are reduced. A longer followup is needed for group 5 before we can adopt vertical banded gastroplasty as the operation of choice.

Our Learning Curve

From group 1, the Roux-en-y gastrojejunostomy, we learned the importance of correctly sizing the proximal pouch and stoma. If either of these is too large, the results are not optimal.

In groups 1, 2, and 3, the greater curvature of the stomach is mobilized leading to a high incidence of splenic injury, splenectomy, and subphrenic abscess. Because the greater curvature is devascularized, there is a tendency for ischemia, leaks, edema, and obstruction.

The gastrogastrostomy partition performed in group 4 allowed us to avoid mobilizing much of the greater curvature and short gastric vessels, thereby reducing the incidence of splenectomy, abscesses and leaks. Long-term weight loss results are not good because of pouch and stoma structure.

The vertical banded gastroplasty avoids most of the technical problems created by the procedures done on patients in groups 1 through 4. The pouch is small at 20-25 ml compared with the 50-60 ml size in the early operations. The partition is secured with a double application of TA-55 staples. Previous experience of one application in 31 pa-

Table 2
Percent Excess Weight Loss Following Five Gastric Operations

Time since operation	GB-RY	GB-Loop	GP	GG	VBG
6 months	41	39	45	40	41
1 year	57	59	65	48	—
2 years	57	62	65	39	—

The first 3 groups of patients (GB-RY, GB-Loop, GP) have been followed from one to five years. Those treated with GG have been followed as long as three years. VBG patients have been followed less than one year.

tients in group 1 showed a 20% failure of the partition. The stoma in the vertical banded gastroplasty is reinforced with a polypropylene mesh to prevent strictures. Earlier procedures used a nonreinforced stoma or a suture-reinforced stoma which frequently would dilate. This is especially true in the patients who had a gastrogastrostomy. In addition, the vertical banded gastroplasty has other technical advantages compared with previous operations. The short gastric vessels are not divided and therefore injury to the spleen is avoided. Although theoretically the wound is contaminated by creation of the gastric window, there is no open anastomosis to provide gross contamination for contributions to abscess formation. The only information lacking on vertical banded gastroplasty is whether or not the patients will have a weight loss comparable to the other operations. Preliminary data from our institution are encouraging. Using a 5.0 cm band, Mason et al. have reported 58% excess weight loss and Doherty has shown a 68% excess weight loss at one year.⁷

Patient selection is as important as the type of surgery. Success is dependent on a well-motivated and cooperative patient. Experience is the major teacher that guides the surgeon to select patients who are cooperative and compliant.

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A "New" Cause of Diarrhea?

Richard A. Davidson, M.D.

FOR the next topic in our series about parasitic infections in North Carolina, I have chosen to discuss an infection that we have not yet documented at North Carolina Memorial Hospital. The reason for this choice is that Cryptosporidiosis is something you will be hearing a great deal more about in the next few years.

Cryptosporidium is a small (4-6 micrometers) protozoan parasite which has been known in veterinary circles for some time as a causative agent of diarrhea in calves, lambs, goats, and poultry. It is in the same suborder as Toxoplasma. Unlike most parasites, Cryptosporidia are not species-specific; organisms recovered from one host have been easily transmitted to other species. The implications of this fact are responsible for the recent interest in the organism.

The life cycle includes both sexual and asexual stages; the organisms attach to enterocytes and undergo maturation. The length of the life cycle seems to be associated with the host's age and immunologic competence; in 1-day old lambs the life cycle may be as short as 72 hours.¹ The size of the organism makes its recovery in stools very difficult unless concentration techniques are carried out. The diagnosis has been made most frequently by biopsy, which shows dot-like organisms imbedded in the brush border of the enterocytes on standard stains.

The first case of human Cryptosporidiosis was reported in 1976.² The overwhelming majority of subsequent case reports consisted of patients who were immunocompromised, most frequently from immunotherapy or congenital immune deficiency syndromes; more recently it has been found in the acquired immunodeficiency syndrome and in patients in high risk categories for AIDS, such as homosexuals, hemophiliacs and Haitians. In some immunocompromised individuals the infection was fatal, with severe uncontrollable diarrhea, dehydration, and electrolyte abnormalities.

In 1982 Cryptosporidia enteritis was reported in a professional baseball player in otherwise excellent health.³ The patient had worked as a horse trainer just prior to the onset of his illness, which was a severe dysentery lasting one month before gradually improving without therapy. Shortly after this report an outbreak of Cryptosporidia occurred in 12 immunocompetent individuals who had direct contact with infected calves during outbreaks of calf Cryptosporidiosis.⁴ The infection was transmitted experimentally to calves and mice from humans.

Two large scale screening studies found a high prevalence of Cryptosporidia in stools of patients with gastroenteritis. Tzipori et al.⁵ in Australia, found Cryptosporidia in the stools of 4.1% of 884 hospitalized patients with gastroenteritis; none of 320 patients without gastroenteritis was excreting the organisms. Jokipii et al.⁶ studied stools sent by general practitioners in Finland. Of 154 stools examined for Cryptosporidia, 14 (9%) were positive. The authors compared the clinical syndrome with giardiasis and found the incubation periods to be similar (median 7 days); the course of the illness was shorter (10 vs. 25 days) and more abdominal pain and cramping were seen in the patients with Cryptosporidiosis. Giardiasis caused more bloating, anorexia, and weakness.

Cryptosporidiosis seems to be largely self-limited in healthy adults, with resolution of the illness within 10 days in half of reported cases. It has been estimated that up to 40% of acute diarrheal illness may be caused by cryptosporidia, especially in more rural areas such as North Carolina. A three-step stool examination, which is more sensitive than biopsy, has recently been described.⁷

Over forty antimicrobials have been tested against the organism without evidence of efficacy. Currently the only therapies that hold promise are spiramycin, a drug similar to erythromycin and clindamycin, and the combination of quinine and clindamycin.⁸ Both regimens were given to AIDS patients with some response, although most patients did not respond to either. Continuing study by medical and veterinary institutions may lead to the development of effective therapy. Knowledge of the mode of transmission of the organism may alert physicians to outbreaks of this infection in persons exposed to farm animals and other persons at risk, and may prevent extended work-ups and inappropriate use of medication.

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From the Department of Medicine, The University of North Carolina, Chapel Hill 27514.

Caffeine — A Drug with Multiple Points of Entry

Gregory C. Khoury, M.D. and Allan A. Maltbie, M.D.

MY interest in caffeine-related problems was aroused by a 42-year-old white nurse who had a seven-year history of psychiatric difficulties. Past diagnoses included anxiety neurosis, hysterical personality, hysteroid dysphoria, and panic attacks. The patient complained of chronic insomnia, symptoms of anxiety, and irritability. She reported spells of palpitations, at times associated with facial flushing and headache with a worsening of symptomatology through the day. Her scholastic and work performance had deteriorated over the preceding seven years. A detailed history revealed that over this interval the patient had been drinking in excess of 12 cups of brewed coffee per day and additionally one gallon of diet cola. For persistent insomnia, she had used a nightly dose of from 15-20 mg of Valium with a partial sleep response. Benadryl and Elavil had been administered without improvement. Over the seven years the diagnosis of caffeinism had not been entertained despite multiple consultations with several physicians. The patient accepted my treatment recommendations to begin short-term psychotherapy and a gradual taper of caffeine intake. Her symptoms dramatically improved with cessation of headaches, palpitations, and symptoms of facial flushing. She became less irritable and was able to sleep. Concentration and work performance improved.

The patient was clinically observed to maintain this symptomatic improvement for a three-week period, during which psychotherapy continued. She then left psychotherapy due to emerging fears of closeness and anger over the upcoming termination. This occurred, however, well after the superimposed caffeinism was diagnosed and treated to full resolution.

The proper treatment of caffeinism is a gradual taper of caffeine with conservative management of any withdrawal symptoms.¹ Withdrawal headaches are best managed with plain aspirin or acetaminophen since caffeine may be an additive in some of the combination agents. The sluggishness and dysphoria of withdrawal generally respond to reassurance and typically abate once the withdrawal process is complete. During the withdrawal taper, ingestion of caffeine after 5:00 p.m. should not be allowed in an effort to prevent insomnia. The complaint of insomnia generally abates quickly with the cessation of evening caffeine, and sedative hypnotics are generally not needed in this clinical situation.

Caffeinism

Caffeinism may be defined as a pathological dependence on caffeine. Here a large volume of caffeine is consumed and associated with symptoms of diuresis, insomnia, hyperirritability, anxiety, weight loss, bouts of flushing and chilliness, headache, palpitations, tachycardia, and mild increase in body temperature. Related psychiatric symptoms include anxiety, depression, psychophysiologic reactions, and even psychosis.^{1, 2} Withdrawal symptoms, which usually include fatigue, sense of dysphoria with headache, and mild confusion with decreased reaction time have been reported. These symptoms of withdrawal are reversed by the administration of caffeine. The degree of severity of symptoms with caffeinism seems directly proportional to the size of the ingested dose of caffeine.

Sources, Dose and Stimulant Effects

Caffeine is ubiquitously available today in a variety of socially acceptable beverages and over-the-counter preparations including coffee, tea, cola drinks, hot cocoa, analgesics, dietary aids, diuretics, and stimulants.

Popular misconceptions exist as to the content of caffeine in many beverages. The most prominent of these is the notion that brewed coffee is twice as caffeine-rich as tea and three times as caffeine-rich as cola drinks.³ In reality, the 2% caffeine content of tea leaves is often higher than that of coffee beans, which ranges from .7% to 2%. Furthermore, once prepared the beverages contain about equal amounts of the alkaloid (100-150 mg per 8 oz cup). Instant coffee contains 86-99 mg/cup and a cola drink contains 25-35 mg/cup or 35-55 mg/12 oz bottle. Substantial inconsistencies occur in the literature as to the amount of caffeine to be found in a cup of brewed coffee. These inconsistencies serve to confuse the correlation between symptom cluster and ingested dose and may contribute to substantial underestimation of the amount of caffeine ingested by individuals.

Caffeine ingestion may cause temporary exacerbation of endogenous anxiety disorders as well as psychotic thought disorders. Freitas and Schwartz⁴ noted the negative effects of caffeine in chronic psychiatric inpatients and published evidence of significant improvement in patient management with reduction of symptoms where caffeine utilization was reduced. After one week of substitution of decaffeinated coffee for regular coffee, patients with manic depressive disorder, organic brain syndrome, and schizophrenia demonstrated significant decrease in hostility, suspiciousness, anxiety levels, and irritability. Return to

From the Department of Psychiatry, Duke University Medical Center, Durham 27710.

regular coffee reversed this improvement and resulted in significant increase in anxiety, somatic concerns, irritability, hostility, and manifest psychotic symptomatology.

Gilliland and Andress⁵ reported a statistically higher incidence of anxiety and depression in moderate and high caffeine consumer groups compared with abstainers. The high consumer group also reported higher levels of symptoms of caffeinism, higher frequency of psychophysiologic disorders and lower academic performance when compared with abstainers.

Greden et al.⁶ reported a statistically significant increase in anxiety and depression symptomatology in high caffeine consumers (750 mg or more) compared with moderate and low consumers. In addition, high consumers reported more problems with physical health and greater use of sedative hypnotics and tranquilizers than did moderate and low consumers.

Victor, Lubetsky, and Greden¹ compared reported somatic symptoms among low, moderate, and high caffeine consumers. Diuresis, insomnia, headache, diarrhea, anxiety, tachycardia, and tremulousness were most commonly reported in descending order of frequency in the study. Differences were common among high, moderate, and low consumers, and dose response associations seemed apparent. This study seemed to confirm the hypothesis of

the dose response death.⁶ Although the lethal dose of caffeine is estimated at 10 grams,⁶ a review of all reported cases reveals fatalities resulting from ingestion of 3 to 50 gm of caffeine. In these fatalities, sources of caffeine included over-the-counter diet aids, concentrated caffeine tablets, triacqua tablets, and erroneous administration of caffeine in sodium benzoate solution by hospital personnel.

A Word to the Wise

Drug histories are notoriously difficult to take. Drugs creep in from every nook and cranny — even in drink and food. Remember caffeine when you are looking for symptoms that may be due to drugs.

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Antitrust and Physician Payment

Michael R. Pollard

THE purpose of this paper is to review antitrust principles and laws as they relate to physician payment. On their face, the antitrust statutes are deceptively simple. Unlike many federal statutes, the antitrust statutes are very brief and written in a relatively straightforward style. However, the body of antitrust law is largely the result of judicial interpretations of those statutes, and the opinions in antitrust cases can be long and complicated expositions of fact, law and economics. Antitrust cases typically raise many factual questions and the resolution of those questions often turns on sophisticated economic analysis of the competitive effects of the business practices under review by the court. Because this paper is intended for a well-informed but essentially nonlawyer audience, it is not heavily footnoted and most statements are not qualified by numerous *caveats* as they would be were it written for antitrust attorneys or economists. My intent here is to inform and guide the interested reader through an area of the law that is increasingly relevant to the issue of physician payment.

I. The Origins and Elements of Antitrust Analysis

A. Historical Underpinnings

Every society must order its economic activity according to a basic framework. Despite a heavy overlay of government regulation, the United States economy is based on the price system and competition. The price system conveys information to both producers and consumers and it creates incentives to produce goods and services efficiently. It also stimulates producers to innovate and offer new services that generate as well as respond to consumers' preferences. In competitive markets, producers will deliver goods and services that the majority of consumers demand. Competitive markets operate on the basis of consent and do not force individuals to act against self-interest.¹ The federal antitrust statutes were enacted to ensure that market competition is not unreasonably restrained by certain private agreements or practices. These statutes attempt to promote vigorous competition among many sellers: they are based on the premise that such a system will foster economic efficiencies. They were not designed to redistribute income or to achieve other social policy goals.

Contemporary antitrust and trade regulation laws find their antecedents in English Common Law.² During the thirteenth century in England, when commerce was primarily confined to local markets, the following activities

were indictable offenses: 1) buying goods before they came to market; 2) buying goods in large quantities and selling them in smaller amounts; 3) buying crops before they were harvested. These were the so-called "middleman offenses": they were grounded in the belief that middlemen raised prices without achieving any useful business or social purpose.

English towns during the fifteenth and sixteenth centuries typically restricted trading by strangers through granting monopolies to local business interests, such as the trade guilds. The English Crown also engaged in granting monopolies as a means of raising revenue. Restraints on trade became so ubiquitous and burdensome that Parliament in 1623 enacted the Statute of Monopolies which invalidated all monopolies with exceptions for patents on new inventions, some monopolies granted by towns and guilds to establish more orderly trade relationships, and Parliamentary grants.³

English Common Law conspiracy doctrines influenced the prohibitions against unlawful conspiracies found in current antitrust statutes. These doctrines condemned otherwise lawful acts if they were committed by several individuals with the intent to achieve an "unlawful" purpose. Unlawful in this context meant "contrary to public policy."

The seeds for the antitrust statutes in the United States were sown during the rapid economic growth of the second half of the nineteenth century. This period spawned tremendous changes in industrial production and transportation, but it was marred by periodic and severe economic depressions. Populism, which arose out of discontent among agricultural and small town interests, gained many supporters and generated pressure for fundamental monetary and business reforms. The incidence of financial scandal and public corruption was high during this period, and many examples involved large trusts and monopolies such as the railroads and the oil companies. Certain markets were controlled by monopolists, but even in those markets where competition did exist, predatory pricing and other unfair business practices were commonplace.

B. The Antitrust Statutes

Despite the scandals and corruption of the late nineteenth century, public sentiment did not favor government takeover of basic industries or even stringent government regulation as the remedy for marketplace abuses. Instead, Congress trusted competition to police the market and free it of abusive private restraints. Accordingly, Congress enacted the Sherman Antitrust Act in 1890 which condemned monopolies and contracts, combinations, and conspiracies that restrain trade.⁴

From the Office of Policy Analysis, Pharmaceutical Manufacturers Association, 1100 Fifteenth Street, NW, Washington, DC 20005. The views expressed here are the author's and do not necessarily reflect the views of the Pharmaceutical Manufacturers Association or any of its member companies.

During the next two decades, the courts relied on the Sherman Act to strike down price fixing by railroads, the merger of two large western railroads, and three large trusts that controlled the meat, oil, and tobacco industries. Violations of Sections 1 and 2 of the Sherman Act are criminal offenses and can be punished by up to one year imprisonment and fines. The Act is enforced by the Justice Department.

In 1914, Congress supplemented the Sherman Act by enacting the Federal Trade Commission Act (FTC Act)⁵ and the Clayton Antitrust Act.⁶ The FTC Act appears to have emerged from both business concerns about the lack of an administrative commission or agency under the Sherman Act to provide guidance on which trade practices were lawful or unlawful, and those who believed business practices needed to be policed by a strong, independent commission with investigative and law enforcement powers. Members of this latter group felt that the Sherman Act was too general in its scope to provide adequate protection from unfair trade practices and that the Attorney General was not sufficiently insulated from political pressure to vigorously enforce a statute that often ran counter to strong business interests.⁷

The Federal Trade Commission Act prohibits "unfair methods of competition" and "unfair or deceptive acts or practices" affecting interstate commerce. Under judicial supervision and congressional oversight, the FTC is free to work out the exact meaning of unfairness or deception in the context of particular cases. In addition, as the result of amendments to the FTC Act in 1975, the Commission is authorized to promulgate trade regulation rules delineating and prohibiting unfair acts or practices on an industrywide basis. This rulemaking authority has embroiled the FTC in several heated controversies with industry groups. The FTC issues cease and desist orders and can impose civil penalties or require consumer redress in certain cases.

The Clayton Antitrust Act was enacted to provide legal remedies for certain practices that were not specifically covered by the Sherman Act. It prohibits 1) price discrimination; 2) sales on the condition that the buyer must stop dealing with the seller's competitors; 3) certain corporate mergers; 4) interlocking corporate directorates; and 5) certain common carrier transactions. The Clayton Act is enforced by both the Justice Department and the Federal Trade Commission, and violations of the Act are civil in nature.

C. Elements of Analysis

The antitrust laws are aimed at "unreasonable" restraints on trade and competition, even though a literal reading of Section 1 of the Sherman Act might imply that all contracts and agreements that restrain trade are prohibited. In the 1911 case of *Standard Oil Company v. United States*,⁸ Chief Justice White first articulated the standard of reasonableness, or "rule of reason," that guides the courts in reviewing the legality of particular trade restraints. The elements of the "rule of reason" test were further elaborated in the case of *Board of Trade of Chicago v. United States*.⁹ Here, the Supreme Court held that the true test of legality for a restraint of trade is whether it merely regulates and promotes competition, or whether it suppresses or

destroys competition. In order to make this determination, courts must review the nature of the business in question, its condition before and after the restraint was imposed, the history of the restraint, and the purposes or ends for which it was adopted.

The "rule of reason," adopted by the Supreme Court more than 70 years ago, is the principle that still guides judges today in antitrust cases. However, it is a somewhat vague standard and it leads to extensive factual analysis, including costly economic studies. Thus, the courts have decided to dispense with a full-blown rule of reason analysis in certain cases involving restraints so blatantly anticompetitive that they are deemed to be *per se* unreasonable and illegal.¹⁰ The courts have held the following activities to be *per se* violations of the antitrust laws: price fixing, division of markets, group boycotts, and tying arrangements.

D. Application of the Antitrust Laws to the Professions

Prior to 1975, the antitrust laws were of little concern to the professions. But, in that year, the Supreme Court struck down a minimum fee schedule imposed by a bar association in the case of *Goldfarb v. Virginia State Bar*.¹¹ The case is significant because the Court rejected the argument that the learned professions were exempt from the antitrust laws and did not engage in "trade" or "commerce" as those terms are used in the antitrust statutes. The Court concluded that Congress did not intend for professionals to be exempt from antitrust scrutiny.¹²

Three years later, the Court ruled on an ethical prohibition on competitive bidding imposed by the National Society of Professional Engineers and reiterated that the professions must comply with the antitrust laws.¹³ The Court emphasized that the primary objective of antitrust is to promote competition and that courts, in reviewing antitrust cases, are limited to making judgments about the competitive impact and economic significance of the challenged restraint. The Court rejected the argument that judges should decide whether competition in a particular context is socially good or bad: the justices said that such questions should be decided by Congress.¹⁴ However, the Court did acknowledge that the professions may merit special antitrust consideration because they do differ from other business services.

These decisions laid the groundwork for numerous investigations of restraints on professional practice by antitrust enforcement agencies, both at the federal and state levels. The Department of Justice has investigated architects, accountants, civil engineers, mechanical engineers, and physicians' specialty societies. The Federal Trade Commission has reviewed restraints imposed by lawyers, accountants, real estate brokers, physicians, dentists and veterinarians. States like Ohio, West Virginia, and Arizona have focused their investigations primarily on health professionals.

The most important law enforcement action brought by the Federal Trade Commission against a professional organization was the *American Medical Association* case.¹⁵ Here, the Commission found that the AMA had prohibited almost all forms of truthful advertising and solicitation

through enforcement of various provisions of its code of professional ethics. Although the Commission found the AMA's restrictions on truthful advertising to be illegal, its opinion in the case states that the "... AMA has a valuable and unique role to play with respect to deceptive advertising and oppressive forms of solicitation by physicians." The Commission's order expressly provides that the AMA may adopt and enforce rules to prohibit such practices.

The FTC's AMA case was also a challenge to the AMA's so-called "contract practice" rules. Under those rules, it was unethical for a physician to sign a contract with a "lay" hospital, or HMO, if there was "underbidding" for the contract, or if the compensation was "inadequate" based on the fees usually charged in the community. These restrictions were, in some respects, quite similar to the rules against competitive bidding that the Supreme Court found illegal in the *Professional Engineers* case. The Commission ordered the AMA to eliminate these restrictions, which they did in their revised Principles of Medical Ethics.

II. Effect of Antitrust on Professional Practice

The fact that the antitrust laws are fully applicable to health professionals does not mean that they cannot engage in self-regulation or that restraints on their conduct will be treated in exactly the same way as a similar restraint on the conduct of a group of businessmen. Certification by medical specialty groups is an example of self-regulation that is reasonable provided the certification criteria and procedures are fair and the certification decisions are made objectively, on the basis of competence. Ethical rules that have the purpose and effect of prohibiting false or deceptive advertising are another example of permissible, in fact highly desirable, self-regulation. Insofar as health and other professional services markets are truly unique, traditional antitrust analysis is sufficiently flexible to take such conditions into account in considering whether a particular practice has had an unreasonably anticompetitive effect.

It is also clear that the antitrust laws do not interfere with state regulation of the professions. In *Bates v. Arizona State Bar*,¹⁶ the Supreme Court rejected an antitrust challenge to restrictions that the Arizona Supreme Court had imposed on attorney advertising. The Court did this because the antitrust laws proscribe certain private actions but do not extend to anticompetitive practices that are sanctioned by the states. The Court has said on numerous occasions that immunity from the antitrust laws is warranted when the anticompetitive activity is conducted pursuant to a clearly articulated and affirmatively expressed state policy that is actively supervised by the state itself: this is the so-called "state action" doctrine.¹⁷

Despite the above mentioned limits on the scope of antitrust scrutiny, whenever professionals seek to influence fees or payment, antitrust concerns will be raised. Following *Goldfarb's* condemnation of minimum fee schedules as price-fixing, two elements of how fees are structured in medical markets became targets for antitrust scrutiny by law enforcement officials — i.e., relative value studies¹⁸ and medical society control of Blue Shield plans.¹⁹

Relative value studies attach a series of numerical

weights to medical procedures. The weights indicate the proportional value of each procedure to all others included in the study. Such tables are not fee schedules, but they can be easily converted to them by multiplying each proportional value by a dollar conversion factor. The Justice Department and the Federal Trade Commission saw the relationship between relative value studies and the illegal pricing formulas used by other industries to set prices, and enjoined them or obtained consent decrees governing their future development and use. More recently, however, a federal district court rejected the argument that a relative value study was a form of price-fixing that constitutes a *per se* violation of the Sherman Act.²⁰ It is not clear how the case would have been resolved had the Justice Department introduced evidence on the adverse economic effects of the scheme and the court had based its decision on a rule of reason analysis.

Medical society control of Blue Shield was, at one time, a target for antitrust enforcement agencies. During the late 1970s, it looked like the Federal Trade Commission might initiate a rulemaking proceeding challenging the medical profession's influence over the policies and practices of Blue Shield plans. This initiative ultimately was abandoned by the FTC, but not before other medically dominated organizations had taken some steps toward including more nonmedical representation on their governing boards.

In the area of physicians' fees and payment arrangements, the antitrust laws clearly prohibit economic boycotts, both maximum and minimum price fixing, and attempts to monopolize the provision of services in a market. The antitrust laws do *not* prohibit professional consultation with health insurers, peer review of professional practices or utilization of hospital facilities, disciplinary actions by professional societies, or the formation and participation in prepaid health care plans where the physicians are sufficiently integrated into the financial structure that they would share in the risk of loss should the plan fail to meet its commitments. The legality of relative value studies, professional participation in peer review of fees, exclusive contract arrangements with hospitals or other institutional providers, and participation in less than fully integrated health care plans is unclear at this time.

III. The Effect of the Antitrust Laws on Insurers

The McCarran-Ferguson Act exempts from the antitrust laws the "business of insurance" to the extent that it is regulated by state law and does not involve acts of "boycott, coercion, or intimidation."²¹ In a series of cases, the Supreme Court has explained and progressively narrowed the scope of this exemption. In *St. Paul Fire & Marine Insurance Company v. Barry*,²² the Court stated that the term "boycott" included concerted refusals to deal with consumers, as well as competitors, within an industry. In *Group Life & Health Insurance Company v. Royal Drug Company*,²³ the Court set out three criteria for deciding whether a practice falls within the business of insurance: 1) the practice must transfer or spread a policyholder's risk; 2) the practice must be an integral part of the policy relationship between the insurer and the insured; and 3) the practice must be limited to entities within the insurance industry. In 1982, the Supreme Court held that the McCarran

ran-Ferguson Act does not remove peer review of professional fees from the purview of the antitrust laws.²⁴ This does not mean that peer review is illegal, but merely that it is not exempt from antitrust scrutiny.

The McCarran-Ferguson Act exemption has been asserted by professionals in the context of antitrust cases when their activities were related to health care financing considerations and, arguably, were part of the business of insurance. While considerable ambiguity continues to exist concerning the scope of this exemption, the Supreme Court's decisions make it clear that it, like all exemptions from the antitrust laws, will be narrowly construed.

For several years, the commercial health insurance companies have asserted that they are unable to compete effectively with Blue Cross/Blue Shield plans in most markets because their market shares are too small for them to bargain aggressively with hospitals or other providers. In order to attain more leverage in these markets, they suggest that they should be able to share data among themselves on costs and utilization but claim that they are precluded from doing so because of the antitrust laws. The insurers never clearly stated just what types of information they wanted to pool and share with their competitors, and they never officially requested either the Justice Department or the Federal Trade Commission to review the matter and provide either informal or formal advice on the legality of such arrangements. In November 1983, Senator Arlen Specter introduced a bill entitled the "Health Care Cost Containment Act of 1983" which, if enacted, would grant antitrust immunity to insurers who collaboratively collect data on health care costs and jointly negotiate prices with hospitals, physicians and other health care providers.²⁵

IV. New Methods for Paying Physicians

Antitrust has long been a tool that proponents of alternative delivery systems have used to ease their entry into traditional health care markets. When traditional fee-for-service physicians have threatened to boycott HMOs or the physicians who affiliate with them, the antitrust laws have been an effective means for stopping such anticompetitive practices from coming to fruition. Similarly, efforts by organized medical groups to discourage price competition or prohibit the disclosure of fees have been successfully challenged under the antitrust statutes. Today, the pressure to curb rising health care costs is forcing even traditional physicians to consider participating in a variety of new organizations that promise to be more cost conscious than older methods for paying physicians but that also preserve most of the characteristics of fee-for-service practice.

The growth and development of these organizations has been concentrated primarily in California and other western states.²⁶ The term "preferred provider organization," or PPO, was coined by InterStudy to describe many of these new physician groups. Although PPOs can be sponsored by underwriters, providers, employers, or others, they seem to share four basic characteristics: 1) insurers or other third party payers contract with a panel of providers to furnish services; 2) a negotiated fee schedule (normally discounted from what the provider usually charges) and a promise to pay the providers promptly; 3) some form of utilization review; and 4) patients are not limited to the PPO panel but

instead are encouraged to use the panel members through incentives such as reduced deductibles or no copayments. PPOs appear to have the potential for creating competition in both the financing and the provision of health care by offering price and coverage options that increase the economic incentives to control fees and utilization levels.

Structuring the fee schedule or discount may pose problems for some PPOs given the Supreme Court's decision in *Arizona v. Maricopa County Medical Society*.²⁷ Here, the Court held that it was *per se* unlawful for physician members of a foundation for medical care to agree jointly on the maximum fees that could be claimed in payment for services rendered to policyholders of foundation-approved insurance plans. For a variety of reasons, the *Maricopa* case has left the law in this area uncertain.

The decision is clear that the peer review and administrative functions performed by the medical care foundations did not prevent application of the *per se* rule; it also clarifies that competitors who have achieved sufficient operational integration by forming some sort of partnership or joint venture can jointly set prices without *per se* condemnation. But, by failing to supply us with an analytic framework, the Court missed an important opportunity to clarify a complex and critical aspect of price fixing law. *Maricopa* does not make it easier to discern when competitors acting in a joint enterprise have sufficiently integrated their operations so that an agreement they reach on price would be analyzed by the courts under the rule of reason as a joint productive arrangement, rather than being automatically condemned as naked price fixing. The Court gave no useful guidance for physician groups that may be willing to integrate more than was evident in *Maricopa*, but who might not wish to go as far as establishing partnerships or other joint ownership arrangements. This uncertainty may discourage the formation of alternative delivery systems with the potential for enhancing price competition and efficiency.

While the Supreme Court's decision in *Maricopa* certainly does not tell us much about what physicians can do in relation to prepayment plans, it surely does not mean that physicians who have achieved significant integration can never control payment decisions in a prepayment plan. Despite *Maricopa*, there are some observations I can make about provider groups and PPOs:

—A group of providers could combine their practices into a single group practice or clinic and serve as the provider component of a PPO.

—A group of providers also could establish an entire PPO by going into the financing and underwriting business (the latter could be accomplished through a joint venture with an insurer).

—*Maricopa* tells us that simply performing certain administrative functions, such as peer review and claims adjustment, does not take joint price setting activities out of the *per se* category of antitrust violation.

V. Summary and Conclusions

The antitrust laws do impose limits on the ability of physicians to engage in joint fee setting and to employ unfair tactics to discourage or penalize competitors. At the same time, antitrust does not favor one method of payment or one type of physician organization over another. Rather,

it is directed toward preserving open and fair competition in the market for health services.

The doctrines and theories of traditional antitrust analysis are expansive and flexible enough to deal with new forms of physician payment that have already been introduced as well as those that are still a gleam in someone's eye. As in other antitrust matters, the following concerns and questions will be addressed if any of the new payment methods are subject to antitrust scrutiny:

—What are the probable *effects* of the challenged practice? Will it enhance or dampen competitive forces in the market?

—What is its *purpose*?

—Who is involved? Are they competitors or are they buyers?

—What is really happening? Is the practice under scrutiny a competitive restraint or is it really ancillary to a larger arrangement that will promote greater efficiency and enhance competition?

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DRGs: A Positive Side to the Ledger

Andrew G. Wallace, M.D. and Phyllis S. Ellenbogen, M.B.A.

IN the fall of 1983, the federal government adopted a prospective payment system to reimburse hospitals for services rendered to Medicare patients. Payment based on prospectively set prices seems likely to be adopted by other third-party groups and may prove to be one of the most significant changes in recent years for health care providers. Because it represents a major change and because it is imposed on us by the external world, it is creating considerable anxiety. Change is always an ordeal and fraught with anxiety; the challenge is to adjust constructively to this important change while preserving those characteristics that are essential and desired in medical practice. The thesis of this editorial is that prospective reimbursement can be viewed as having many advantages to medical practice. We must seize this opportunity to take advantage of its potential benefits for clinical research, education, and patient care.

Physicians are trained to be knowledgeable about the behavior of biological systems, all of which are governed by the principles of feedback control. We have learned about these principles as they affect enzyme systems, cell growth, and the operation of all major organ systems in the body. At another level, we are accustomed to these principles in our everyday dealing with patients and colleagues, who give us feedback that helps us evaluate our relationships.

The implementation of prospective payment systems is simply an example of feedback at yet another level, namely the political level. Whether we are engaged in patient care, in research, or in training, these activities are highly private in character but clearly public in purpose. Because of both the benefits and cost, activities of the medical enterprise are a matter of public policy. Prospective payment is being implemented by the government in response to the health care expenditures that exceeded \$300 billion in 1983 and, even more importantly, because the health care bill has been increasing at twice the general rate of inflation for the past decade. In decreasing order of resource consumption, hospitals, physicians' fees and nursing homes represent the major components of the health care bill and hence they are the major focus of the feedback forces that are designed to control the rate of increase of that bill.

Government is the major current initiator of the effort to control health care costs. This is because it pays approximately 40% of the total health care cost and about 55% of hospital costs through its role in the Medicare and Medicaid programs. Business is the second largest participant in paying health care costs through contributions to the health care fringe benefit program of employees. Government and

business have formed an alliance in their effort to control the rate of increase of hospital bills.

Prospective reimbursement became a reality in the fall of 1983 when the government passed amendments to the Social Security Act calling for the implementation of a prospective reimbursement system based on diagnostic related groups (DRGs). The bill was passed with remarkable speed and by a heavy majority and will be in effect at all hospitals by July 1984.

The strategy of the DRG-based prospective reimbursement system is basically to change the incentive. With retrospective reimbursement of either charges or costs, the incentive to hospitals has been to do more and as a consequence to escalate health care costs in general. Prospective reimbursement essentially states that the payor, in this case Medicare, will provide a fixed payment for the treatment of a given episode of illness. If the hospital spends more than the payment, it is at risk; if the hospital spends less, it has the opportunity to share with the government in the savings.

The government's prospective payment system is based on prices for each of 467 different DRGs. The DRG is simply a classification system that was developed during the 1970s at Yale and then further tested and refined with the Medicare data base. The system first classifies each episode of illness into one of 23 system-specific major diagnostic categories, based on principal diagnosis. Within each major diagnostic category there are several DRGs. These retain elements of clinical coherence and further divide cases, using such information as the principal diagnosis, secondary diagnosis, whether or not an operating room procedure is carried out, age and discharge status of the patient. Hence, a patient with valvular heart disease treated medically would be in one DRG; another with valvular heart disease who underwent cardiac catheterization would be in a second DRG; and still another with valvular heart disease involving catheterization and surgery would be in a third DRG. Based on past records, average costs per DRG have been calculated and used as a basis for setting future levels of reimbursement for an episode of illness.

The DRG system is not a perfect classification scheme and is often criticized because it was not optimally designed to distinguish between subtleties of severity of illness. Let's look for a moment, however, at some of the assets of the system and advantages that it can represent to a hospital and its medical staff.

First of all, the DRG system will increase substantially the effort that the hospital and the medical staff put into the accurate classification of patients discharged from the hospital. As a consequence, we will have much better data

regarding case mix for each hospital, for each clinical department, for each division within departments, and for each individual physician. To an extent never before possible we will be able to answer the question, who does what?

The clinical data base upon which the DRG classification system is based will now be coupled to the patient accounting system. Hence, it will be possible to aggregate charges by DRG and to know what the costs were to the hospital during any given year to manage patients within each DRG. This will give the hospital an idea of where its resources are being spent and can provide an important management tool to the hospital and to the medical staff.

The linking of clinical and financial information for management purposes under prospective reimbursement provides a new opportunity which has not been readily available in the past. Charges for a given episode of hospitalization can be accumulated, categorized by cost center, and reported to the physician more or less in an on-line fashion. It will be possible to know on a daily basis how much has been spent for a hospital room, for laboratory services, for radiology services, for the operating room, for physical therapy, and for any categories of charge within these typical cost center areas. Those charges can then be compared with certain normative data regarding similar cases managed by the same doctor, or at the same institution, or nationally. In this way, financial data can be looked upon as just another laboratory report. In the present climate most physicians are interested in the hospital bill and they are interested in contributing to a reduction in cost as long as that does not compromise their perception of quality patient care. The ability to treat financial data as one would treat any other laboratory variable will provide the doctors with the financial data they seek and will produce a level of awareness regarding expenditures that has the potential of exerting a very favorable influence on the rate of expenditures.

In its simplest form hospital charges can be viewed as a function of both length of stay and the intensity of services rendered a given episode of illness. Thus, efforts to reduce the rate of increase of costs will surely focus on these two

principal areas. Hospitals and doctors are now given an incentive to reduce length of stay. Obvious steps can be taken to achieve this objective by focusing on better scheduling during the first 24 to 48 hours of hospitalization, better scheduling and response time for consultations and procedures within a period of hospitalization, and better discharge planning. An important corollary challenge is to make better use of weekend time when hospitalization over a weekend is required. There is no doubt that significant cost savings can be achieved without any threat to the quality of patient services by focusing on such areas.

The intensity-of-services issue represents another important challenge. The new reimbursement system places greater emphasis on clinical research which evaluates benefits and costs of the intensity of services. Most of us would not disagree that there is redundancy within diagnostic testing, that many patients remain connected to physiological monitors beyond the point when clinically useful information can be obtained, that expensive antibiotics are used in some situations in which less expensive drugs would suffice, and that very expensive blood products are occasionally used when whole blood would achieve the same objective. For the last decade or two we have been exposed to the principles of decision analysis as it applies to the diagnosis of the clinical problem or its treatment. There is now a financial incentive to augment that type of clinical research and to apply it in clinical practice.

The circumstances described above demonstrate a new shared purpose between the hospital and its medical staff. The hospital and its information system can become a research resource for the clinical staff and the hospital can become an arena for the clinical staff to implement the results of operational research. We believe that patient care and teaching will benefit from this approach and that cost savings will be a dividend of the effort. If hospitals and their medical staffs can work together and if the new prospective payment system and its related classification scheme can be viewed more as an asset than a threat, objectives can be reached that are in the mutual interest of clinical practice, training, and cost control.

An added complication... in the treatment of bacterial bronchitis*

Increasing incidence
of ampicillin resistance in
Haemophilus influenzae

Ampicillin Resistant
Haemophilus influenzae

H. influenzae

S. pneumoniae

Brief Summary—Consult the package literature for prescribing information.

Indications and Usage Cefaclor* (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae* (*Diplococcus pneumoniae*), *Haemophilus influenzae*, and *S. pyogenes* (group A beta-hemolytic streptococcus). Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Cefaclor.

Contraindication Cefaclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings IN PENICILLIN SENSITIVE PATIENTS: CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES.

Antibiotics, including Cefaclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Pseudomembranous colitis has been reported with virtually all broad spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life-threatening.

Treatment with broad spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be ruled out.

Precautions **General Precautions**—If an allergic reaction to Cefaclor occurs the drug should be discontinued, and if necessary the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

Prolonged use of Cefaclor may result in the overgrowth of non-susceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross matching procedures when anti-globulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

Cefaclor should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

As a result of administration of Cefaclor, a false positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinette* tablets but not with Tes-Tape* (Glucose Enzymatic Test Strip, Lilly).

Broad spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Usage in Pregnancy—Pregnancy Category B—Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Cefaclor. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response this drug should be used during pregnancy only if clearly needed.

Nursing Mothers—Small amounts of Cefaclor have been detected in mother's milk following administration of single 500 mg doses. Average levels were 0.18, 0.20, 0.21, and 0.16 mcg/ml at two, three, four, and five hours respectively. Trace amounts were detected at one

Some ampicillin-resistant strains of *Haemophilus influenzae*—a recognized complication of bacterial bronchitis*—are sensitive to treatment with Cefaclor.¹⁻⁶

In clinical trials, patients with bacterial bronchitis due to susceptible strains of *Streptococcus pneumoniae*, *H. influenzae*, *S. pyogenes* (group A beta-hemolytic streptococci), or multiple organisms achieved a satisfactory clinical response with Cefaclor.⁷

ceclor®
cefaclor
Pulvules®, 250 and 500 mg

hour. The effect on nursing infants is not known. Caution should be exercised when Cefaclor (cefaclor, Lilly) is administered to a nursing woman.

Usage in Children—Safety and effectiveness of this product for use in infants less than one month of age have not been established.

Adverse Reactions Adverse effects considered related to therapy with Cefaclor are uncommon and are listed below.

Gastrointestinal symptoms occur in about 5 percent of patients and include diarrhea (1 in 70).

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely.

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100), pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis, arthralgia and frequently, fever) have been reported. These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Cefaclor. Such reactions have been reported more frequently in children than adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.

Cases of anaphylaxis have been reported; half of which have occurred in patients with a history of penicillin allergy.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic—Slight elevations of SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematologic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal—Slight elevations in BUN or serum creatinine (less than 1/500) or abnormal urinalysis (less than 1 in 200).

(06178)

*Many authorities attribute acute infectious exacerbation of chronic bronchitis to either *S. pneumoniae* or *H. influenzae*.

Note: Cefaclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

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Some Reflections on the Relationships Between Universities and Industry As They Influence the Evolution of the Medical-Industrial Complex

Stuart Bondurant, M.D.

THERE is an evolving relationship between American universities and industry of which the relationship between schools of medicine and industry is an important subset. Since this medical industrial complex is a significant influence on American medical schools and on American industry and since it will likely influence both medical education and medical practice, some of the developments and events deserve recognition and reflection. Most research universities and research intensive medical schools have had a variety of relationships to industry for many years. Since our universities and our medical schools are a principal source of new knowledge in our society and since new knowledge is today the economic equivalent of a new continent 400 years ago, it is to be expected that there will be great social value in coupling the sources of new knowledge to the business and industrial machinery that applies the new knowledge. I believe that our national interests are best served by a coupling of the generation of knowledge in our universities and medical schools with the application of knowledge in business and industry provided that the rules of the relationships between universities and industries are such that the values and integrity of both parties are respected and preserved. Among the universities and the medical schools of the United States today, there exists a large range of different relationships with industry and there is a rapid change in the nature of many of these relationships. Some institutions, especially those that are not research intensive, have very few relationships to industry of any kind. Others, both public and private, are building new and different relationships on a base of more than a half century of experience in these relationships. Most institutions fall between these extremes and are now developing patent policies, guidelines for faculty involvement with industry, and programs often being called "technology transfer." Enlightened leaders of industry are negotiating arrangements that seem responsive to the needs of the academic partner.

As the nation's medical schools both public and private broaden their relationships with industry, their students and faculty will be influenced by these relationships. For this reason it is worth considering briefly some of the issues that surround these relationships and are now being addressed in various ways in different institutions.

From the perspective of the university and the medical schools, the most important issue can be summarized as that of academic integrity. The very keystone of the academic world is the commitment to an unfettered search for truth and unfettered dissemination of information. The requirement of industry to focus the search and to control the dissemination of knowledge must be reconciled with the fundamental academic value. Most agree that there are ways in which this can be done given the autonomy and scope of the university and its faculty.

A second requirement for academic integrity is the unqualified commitment of the faculty to the purposes of the institution. Insofar as the purposes of the sponsoring industries are not congruent with the purposes of the institution, academic integrity is challenged by the relationship. Again, most believe that there are ways in which the relationship can be defined such that the commitment of the faculty to the purposes of the institution is not compromised.

Third, academic integrity requires that the students perceive that their interests are not compromised within the purposes of the institution.

Fourth, academic integrity requires that the supporters and the sponsors of the institution have confidence in the financial integrity of the institution such that it has not been "bought."

Fifth, academic integrity requires that the institution be recognized as having a high order of competence in its fields of interest and that it is a fertile source of creative scholarship addressed toward important and nontrivial issues. Insofar as the interests of industry may be directed toward short term and highly specific work of little general relevance, the academic institution loses integrity by sacrificing its commitment to scholarship to these goals of industry.

Sixth, academic integrity requires that the educational programs of the institution extend reasonably to the leading edge of the disciplines taught as understood currently. By bringing fundamental and applied questions at the edge of the disciplines into the academic world, relationships to industry can help to enhance academic integrity.

I can speak less knowledgeably of the issues that are of concern to industry. Among these issues, however, are the fiduciary responsibility of the management to the stockholders which means that the ultimate purpose of the corporation must be served by every corporate commitment.

From the School of Medicine, University of North Carolina, Chapel Hill 27514.

The issue of property rights in the knowledge or materials produced as a result of a relationship between industry and the university or medical school is a part of every such relationship. This is especially true when there are multiple sponsors of a program as, for example, in a state institution where a research program is jointly sponsored by the federal government and one or more industries. All parties prefer that the issues of property rights be as simple as possible and this fact tends to limit participation and collaboration within the institution contrary to the classical values of academe. A third issue for industry is that of ethics and corporate behavior in working with universities and medical schools which have different practices and principles. Some industries have in effect adopted the principles and practices of the universities and medical schools for the purposes of their dealings with the universities and the medical schools while other industries have applied to the medical schools and universities the same business practices they would apply to a competitor or a subcontractor.

A set of issues concerns the relationship of faculty to the medical schools and universities as their relationships to industry change. At the heart of these issues are the definitions of conflicts of interest and conflicts of commitment. These issues are illustrated by the many examples of faculty ownership or officership in corporations working in fields related to the work of the faculty member in the university. Short of ownership or officership by members of the facul-

ty, the role of the faculty as consultants to industry, including the amount of time spent and the terms and conditions of the consultancies, bear upon the effectiveness with which the faculty can fulfill their responsibilities to the medical school or to the university.

The foregoing list of issues is imposing. They are being addressed with apparent success by a number of institutions in a number of different ways.

The research enterprise of this nation has evolved to be based largely in the universities. As compared with basing biomedical and other research in freestanding research institutes, placement in the universities and medical schools has the substantial potential advantage of better assuring appropriate brain power to further the research enterprise in generations to come. A principal disadvantage of siting the research enterprise largely in the nation's academic institutions is the attenuation of the relationship between research and application. In my view, it would be a mistake to resist the growing articulation of the teaching and research enterprise of the nation's medical schools with industry. Rather, just as our schools have in times past risen to the challenge of helping to assure access to health care and the availability of quality health care, I believe that we should now accept our responsibility to strengthen the relationships and pathways that bring new knowledge into practice through purposefully structured relationships between industry and universities and medical schools.

North Carolina Medical Journal

Features for Patients

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Learning Disability

Robert J. Thompson, Jr.

Why can't Susan learn?

Why can't Johnny read?

Understanding why children have difficulty with educational tasks and finding ways to help children learn present major challenges to parents, teachers, and health care providers. There can be little doubt that a child's ability to learn influences his or her adjustment in our society. Those who have difficulty in learning can experience considerable stress and their difficulty can be as much of a handicap as any other handicap. If the learning difficulty becomes chronic, the person can indeed be disabled.

Difficulties in learning can arise for numerous reasons. Some are associated with disorders of the brain and central nervous system. Children with mental deficiency or mental retardation have difficulty in learning because of deficits in intellectual functioning. Children who are blind or deaf also experience learning difficulties related to the impairment of their visual or auditory capabilities. Children with major emotional or behavioral problems related to environmental factors may also demonstrate learning difficulties that arise from being distracted, preoccupied or

otherwise "unavailable" to profit from customary educational experience. For some children, learning difficulties are related to a constellation of poor health and educational opportunities.

Children with learning problems that are associated with or "secondary" to other disorders or situations have various intervention or remediation programs available to them. For example, there are special education programs to help children with mental retardation, blindness, or deafness learn to the fullest extent of their capabilities.

Gradually over the last 20 years, there has been an emerging recognition of the existence of children who do not learn normally but whose learning problems are not secondary to other known disorders. With these children, there is a discrepancy between learning performance and presumed capacity. These children seem to have peripheral and central nervous systems that function properly and to have adequate opportunity for learning, but they do not learn according to expectations. From these gradually emerging recognitions and differentiations has come the concept of the child with a learning disability, that is, a child whose learning difficulties are not "secondary" to another disorder, but are "primary."

While the concept of learning disability appears clear, determining what a learning disability is, what causes it, what to do about it, and who is and who is not learning-disabled has generated much confusion and controversy to the consternation of parents, clinicians, legislators, and researchers. Some of the confusion has arisen from the multidisciplinary nature of the field. Psychologists, speech and language clinicians, special educators, pediatricians, physical and occupational therapists, neurologists, ophthalmologists, optometrists, and lawyers all have contributed their diverse disciplinary perspectives and techniques. Also contributing to the confusion has been the lack of an agreed upon definition, classification system, and diagnostic criteria. In a recent review of 408 studies, for example, it was discovered that over 1400 diagnostic techniques had been used to select or describe learning disabled children!¹ Finally, it often appears that there must be at least as many remediation programs or treatment approaches for the child with a learning disability as there are diagnostic approaches. Two points about which there has been particular confusion have been the definition and the role of emotional problems in learning disabilities.

From the Division of Medical Psychology, Duke University Medical Center, Durham 27710.

How Is Learning Disability Defined?

Numerous definitions of learning disabilities have been proposed. Some of these definitions have been incorporated into federal and state legislation affecting services for handicapped children. In the 1973 congressional hearing on the Developmental Disabilities Act, learning disabilities were defined as:

A disorder in one or more of the basic psychological processes involved in understanding or in using language, spoken or written, which disorder may manifest itself in imperfect ability to listen, think, speak, read, write, spell, or do mathematical calculations, and such disorder may include such conditions as perceptual handicaps, brain injury, minimal brain dysfunction, dyslexia, or developmental aphasia, but such term does not include learning problems which are primarily the result of visual, hearing, or motor handicaps, or mental retardation, or emotional disturbance or of environmental disadvantage.²

A similar definition was included in Public Law 94-142 — The Education for All Handicapped Children Act of 1975 which assures a free and appropriate education for all handicapped children. In addition to the number of definitions and lack of consensus, there are other problems associated with the definition. Both the concept and the definition have broadened over the years resulting in an overly inclusive category that lacks meaningfulness. Many definitions are circular and exclusionary to the point that they say more about what a learning disability is not than what it is. Finally, many definitions have focused almost exclusively on deficits within the child to the exclusion of environmental factors and the interaction of environmental factors with factors within the child.

Some of these concerns were addressed in the definition proposed in 1981 by the National Joint Committee for Learning Disabilities repre-

senting a number of professional organizations:

Learning disabilities is a generic term that refers to a heterogeneous group of disorders manifested by significant difficulties in the acquisition and use of listening, speaking, reading, writing, reasoning or mathematical abilities. These disorders are intrinsic to the individual and presumed to be due to central nervous system dysfunction.³

However, this definition also emphasizes intrinsic factors to the exclusion of environmental factors.

Just as there have been many proposed definitions, there are also multiple classification systems to group various subtypes. Learning disabilities have been classified by area of the problem: dyslexia — reading problem, dyscalculia — math problem, dysgraphia — writing problem; and by channel of difficulty: auditory perceptual or visual perceptual; and by impaired processes: discrimination, integration, and sequencing. With various definitions and classification systems, it is not surprising that estimates of the number of learning disabled children also have varied considerably from 1% to 4% of the school age population.

While the definitional problem still exists, advances have been made in understanding through research that should provide the foundation for further systematic research regarding the nature of learning disabilities and their prevention and treatment. First, it is now recognized that learning disability is an umbrella category for a very heterogeneous group of children. Any group of learning disabled children is likely to contain children who have learning difficulties because of a variety of problems. Second, a common problem in learning disabilities is one of processing — that is, using spoken or written language. By processing is meant attending to, encoding or taking in, storing, decoding, and retrieving information. Third, the nature of these

processing difficulties is as yet imperfectly understood but is thought to be related to structural abnormalities in the parts of the brain responsible for processing information. Fourth, research efforts are being focused on establishing the manner in which processing disabilities actually affect performance on school tasks. Fifth, once the relationship between processing disabilities and academic deficits has been ascertained, remedial strategies that are responsive to individual differences in processing skills can be developed.

Learning Disability and Emotional and Behavioral Problems

For many years there was a tacit assumption that learning disorders and emotional problems were related. This assumption influenced both diagnostic and intervention procedures. In many child clinics, it had become habitual to assume a psychological basis for a child's learning problems when no easily recognizable organic basis could be found. However, evidence has now accumulated about the influence of neurological as well as psychological factors in learning problems that illustrates the gross inadequacy of conceptualizing learning disorders as simply a manifestation of an underlying emotional disturbance.

What has resulted is a more considered view. Some children with learning problems do exhibit neurotic fears and traits. Some children fail to learn and exhibit behavior problems because of a primary emotional problem stemming from organic or environmental factors. For other children, the emotional problems are secondary and can best be understood as a result of the interaction of inadequately developed primary skills and environmental stresses that can interfere with psychosocial development and adversely influence the child's developing self concept. The probability that a learning-disabled child will develop emotional or behavioral problems is related to many variables such as

severity and chronicity of the problems, age, sex, subcultural group, socioeconomic level, and intelligence. Many learning-disabled children do cope well. However, all learning-disabled children encounter serious obstacles to adjustment, and their emotional demands and stresses exceed those of most children.

Learning-disabled children have the same basic needs and drives as other children, such as the need for acceptance, adequacy, competency, and mastery, but their handicap sometimes obstructs the satisfaction of these needs and drives. When this occurs, adjustment is threatened and emotional and behavioral problems may develop. The expression of these problems is varied. That is, there is no single reaction pattern or syndrome of behavior common to the learning-disabled population.

However, there are some commonalities. Because of the cognitive-perceptual-motor difficulties, the child can be viewed as vulnerable. This vulnerability can lead to learning and behavior problems that influence the reaction of persons in close contact with the child. Frequently, these significant persons (parents and teachers) can respond with blame and criticism that increases stress and feelings of frustration and tension. Poor self-image can result from failures and from the feedback that the child receives from others. Feelings of inadequacy and a poor self-concept are likely to prolong dependency and immaturity and the utilization of immature defense mechanisms, such as projection of blame and avoidance. This avoidance of tasks impairs motivation and causes a further deficit in skills because certain skills must be practiced to be learned. Thus, there is a lack of improvement, which perpetuates this vicious circle.

A number of studies have used behavior checklists to assess the nature and extent of behavior problems with children with educational problems which range from those requiring special educational programs to

those who are "mainstreamed." The findings indicate that the behavior problems in these special groups are very similar to those found in the general population and in other clinical subgroups: personality problems, conduct problems, and inadequacy/immaturity. Most studies report that the special educational subgroups have higher levels of all three behavior problems than children without learning problems. In addition, contrasts are frequently made with respect to the extent of behavior problems among subgroups of children requiring special education, such as children with mental retardation, learning problems, and emotional problems. The findings are not always consistent with respect to the relative frequencies of each of the three behavior problems. However, the studies do reveal higher levels of behavioral disturbance among children with emotional problems than among those with primary learning problems (learning disabled and mentally retarded). Those with primary learning problems demonstrate higher levels of behavioral disturbance than children without learning problems but differences between mentally retarded and learning disabled subgroups are inconsistently reported.

Views about the association of learning disabilities and emotional and behavioral problems influence service programs. There has been a reliance upon categorical models based upon an either/or theory of etiology; that is, conceptualizing school maladjustment either as a learning problem or as an emotional problem. This has resulted in some benefits, such as classes for learning disabled and for emotionally disturbed children. However, the underlying continuum has been obscured.

What has been needed is a model that integrates an understanding of personality variables with other functional impairments. The model of secondary emotional problems as outlined above with its focus upon environmental factors interacting

with vulnerabilities is one model that offers the potential for developing programs that meet all the needs, primary and secondary, of the child.

What is Dyslexia?

Children experiencing primary learning problems in reading are frequently referred to as dyslexic. Those who have learned to read with little difficulty took reading pretty much for granted. Reading is, however, a very complex cognitive-auditory-visuo-spatial process. It involves integration of several input, output, and mediating processes, visual perception and discrimination and cross-modal integration — the translation of visual symbols into meaningful auditory equivalents.

The two frequently used reading instruction methods are based on the visual and auditory processes underlying reading. The whole-word or "look-say" technique is based on a visual whole. The phonetic technique relies upon the child's analytic and synthesizing abilities in separating words into their phonetic components.

Any failure to learn or retardation in learning this complex reading process can be considered as dyslexia. Reading retardation occurs whenever there is a significant discrepancy between the actual reading level of a child and the reading level expected based on that child's mental age. The amount of discrepancy typically required to be considered dyslexia is 2 years.

Several researchers have identified subgroups of dyslexic children based on functional processing difficulties. One subgroup of dyslexic children comprises those who have difficulty in symbol-sound integration resulting in difficulty developing phonetic word analysis-synthesis skills. Another subgroup of dyslexic children has a primary deficit in the ability to perceive letters and whole words as whole visual configurations. There is another subgroup of dyslexic children who demonstrate deficits in both phonetic word analysis-

sis-synthesis skills and visual perceptual skills. Evidence suggests that the phonic based deficits are more frequent than the visuo-perceptual deficits.

Separating children into groups according to the type of processing difficulty they exhibit allows the development of useful procedures specific to each group. For example, for the child with phonetic-based dyslexia, phonetic skills will be difficult to learn and whole word techniques could prove to be more effective. For children with visual dyslexia, a phonetic approach can be used. For children with both phonetic and visual dyslexia a tactile-kinesthetic approach may be necessary.

Appropriate and meaningful subgroup formation based on causal and functional findings provides the opportunity to develop deficit-specific treatment approaches and to accumulate knowledge about what works best with whom. Much of the progress in this area will of necessity be gained through trial and error. Theory will no doubt guide the exploration but much is to be gained from systematically studying how successful teachers of learning-disabled children achieve their successes so that these remediation skills can be taught to other teachers.

Services for Learning Disabled Children

With learning disabilities as well as other disorders those affected with the disorder require attention now even though we still have quite imperfect understanding. Service programs have evolved to meet the needs of children with learning problems and their families. If parents are concerned about their child's overall level or rate of learning or about specific learning problems in reading, writing, or math, these concerns should be brought to the attention of their school system and their physician. Most school systems have screening and/or educational diagnostic services available to help identify academic problems. Pedia-

tricians and family physicians are increasingly attending to learning and behavioral problems in children as well as to customary health problems. The pediatrician or family physician can play an essential role in providing for additional diagnostic assessment and in helping to implement and coordinate an overall remediation plan.

With a suspected learning problem, obtaining a comprehensive multidisciplinary evaluation involving a team approach of physicians, psychologists, speech and language clinicians, special educators, and physical and occupational therapists is essential. This comprehensive approach is necessary to determine the level and adequacy of the function of various systems in the child and his/her family and school environment that are involved in the learning process. The results of this comprehensive evaluation process serve as the basis for a remediation plan that will involve the educational services of the school and result in an individual educational plan (IEP) for the child. This IEP is developed by the school system in conjunction with the parents and sets specific goals and intervention strategies. Depending upon the results of the comprehensive multidisciplinary assessment process, other services, such as speech and language therapy, medication or psychotherapeutic assistance may also be needed. If so, it is important for all these services to be coordinated and for the overall treatment plan to be monitored in terms of the progress being achieved. Periodic reevaluations may be necessary to update the intervention plan. The pediatrician or family physician can be helpful with these coordinating and monitoring tasks.

North Carolina is fortunate in having a number of resources available to families for comprehensive multidisciplinary assessment of children with learning disabilities. This type of service is available at the major medical centers such as the Duke Developmental Evaluation Center

which is funded by the North Carolina Department of Human Resources through a contract with the Department of Pediatrics at Duke University Medical Center. In addition, the North Carolina Department of Human Resources supports a system of 18 other Developmental Evaluation Centers across the State where comprehensive multidisciplinary evaluations of children with suspected developmental or learning problems can be obtained. Further information about services for learning disabled children can be obtained from your local school system and from the Developmental Evaluation Center that serves your county. Information can also be obtained from the North Carolina Association for Children and Adults with Learning Disabilities, P.O. Box 585, Wilmington, NC 28402, 919/763-0658.

North Carolina is fortunate also in having a number of remediation resources available for children with learning disabilities. There are two primary sources for these services. The public school systems have specially trained teachers who provide remediation for learning-disabled children through special classes and through learning disability resource experiences. Another source of remediation is through the services offered by specific learning disability centers such as the Hill Learning Development Center in Durham.

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Developmental Evaluation Centers in North Carolina

Developmental Evaluation Center
5 Frederick Street
Asheville 28801
704/254-8876

Developmental Evaluation Center
N.C. State Employees' Credit Union
Boone 28607
704/264-1280

Division of Disorders of
Development and Learning
Biological Science Ctr., Box 523
University of North Carolina
Chapel Hill 27514
919/966-5171

Developmental Evaluation Center
3500 Ellington Street
Charlotte 28211
704/372-7790

Developmental Evaluation Center
304 Winecaff School Road
Concord 28025
704/786-9181

Developmental Evaluation Center
Western Carolina University
Cullowhee 28723
704/227-7490

Developmental Evaluation Center
Duke Medical Center
2213 Elba Street
Durham 27705
919/684-5513

Developmental Evaluation Center
P.O. Box 189
Elizabeth City 27909
919/338-2167

Developmental Evaluation Center
3403 Melrose Road
Fayetteville 28304
919/486-1605

Developmental Evaluation Center
2311 W. Cane Blvd., Suite 143
Greensboro 27408
919/282-1100

Developmental Evaluation Center
East Carolina University
P.O. Box 2711
Greenville 27834
919/757-6921

Developmental Evaluation Center
Landco Bldg., 121 N. Sterling Street
Marganton 28655
704/437-2947

Developmental Evaluation Center
Homestead Sq., 2717 Neuse Blvd.
New Bern 28560
919/633-0775

Developmental Evaluation Center
3325 Executive Dr., Suite 110
Raleigh 27609
919/733-6895

Developmental Evaluation Center
111 Medical Arts Mall
Rocky Mount 27801
919/443-8858

Developmental Evaluation Center
Professional Ctr. No.
804 N. Lafayette Street
Shelby 28150
704/482-4416

Developmental Evaluation Center
107 E. Ashe Street
Wadesboro 28170
704/694-5186

Developmental Evaluation Center
1920 South 16th Street
Wilmington 28401
919/762-1744

Developmental Evaluation Center
Bowman Gray School of Medicine
3325 Silas Creek Parkway
Winston-Salem 27103
919/765-9916

Hill Learning Development Center

An Approach to Remediation of Learning Disabilities

Margaret Sigmon, M.Ed. and Wendy Speir, M.Ed.

The Hill Learning Development Center (LDC) was established in 1977 to provide an intensive program to students with specific learning disabilities. Begun as an adjunct to the existing programs of Durham Academy, the LDC was dedicated to founder George Watts Hill in 1980 and became an integral part of Durham Academy. It is now one of the five schools that compose the Academy structure.

The purpose of the LDC is to provide the intensive, specialized, and supportive education needed by learning disabled children to gain academic skills and learning strategies that enable them to return to the regular classroom as successful, independent learners. Through systematic multisensory instruction, the LDC strives to assist each individual in realizing his/her potential through developing strengths, remediating weaknesses, and experiencing success.

In addition, the LDC provides support and assistance to parents through workshops, educational programs, and frequent communication between home and school. The Center is also committed to promoting public awareness of learning disabilities and to serving the community through lectures, teacher-training workshops, and consultation with personnel in the area schools. On-going training is provided to the LDC staff members in the alternative teaching methods that allow mastery of basic skills. The LDC cooperates with nearby universities in providing sites for observation and placement of students in teacher-training programs.

The Admissions Process

Students applying to the LDC program must have been diagnosed as learning-disabled by a licensed psychologist. Such evaluations may be carried out by psychologists within the school system or in private practice. Diagnosis as learning-disabled is based on average or above average intelligence with a discrepancy between aptitude and current achievement in the classroom and no primary emotional disturbance. Students enrolled in the LDC program may demonstrate difficulty in reading, spelling, mathematics, handwriting, organization of written language, or any combination of these areas. These learning disabled students may or may not qualify for resource help in the public schools according to the North Carolina state guidelines.

The application procedure requires that forms be completed and returned by the parent, physician, psychologist, school personnel, and teachers or close friends who know the child outside of the classroom. An educational evaluation is conducted at the LDC in order to meet the applicant, assess academic achievement, and analyze strengths and weaknesses in the learning process.

The Academic Program

Approximately seventy students (preschool through high school) are enrolled in classes at the LDC for a portion of the school day while also attending local public or private schools for the remainder of the day. Full-day placement at the Center is provided for a limited number of elementary students when deemed appropriate.

Students in preschool through high

school may attend the LDC to earn credits in basic language arts and math. Junior and senior high students are also offered instruction in a foreign language, algebra, geometry, English grammar and composition. Transfer credits and grades are issued for students in grades seven through twelve.

Enrollment at the LDC is generally short-term. In most instances necessary remediation may be accomplished in one-and-a-half to two years and students are able to return to their regular schools on a full-time basis. Emphasis may be on either remediation of basic skills or compensatory education.

Based on information acquired from psychological and educational evaluations, specific instructional objectives are written for each individual. These objectives, similar to an IEP or Individual Educational Plan in the public schools, constitute the curriculum for that individual and are revised each semester based on the progress made during that period.

Certified teachers, who have participated in extensive in-service training at the LDC, work with three students in a group who have been carefully selected on the basis of skill level, age, and compatibility.

Progress is reported throughout the school year in the form of instructional objectives, written interim reports, grades, and scores from pre- and post-testing. Parent conferences are scheduled at least twice during the school year and may occur more frequently upon request.

Typically, the half-day program consists of two hours of instruction in the language arts area and one hour of mathematics instruction. Language arts is separated into decoding

From the Hill Learning Development Center, 3130 Pickett Road, Durham 27705.

(reoding) and encoding (written language) classes. Decoding consists of word attack, oral reoding, and reading comprehension while encoding includes spelling, hondwriting, and composition.

While no single approach to teaching reoding is used exclusively, a highly structured phonetic system (based on the Orton-Gillinghom approach) has been particularly successful in teaching students to read, write, and spell.

Math instruction follows a format similar to language arts instruction since the LDC uses a language based approach where work with all symbols is considered a language process. Moth class includes memorization of basic facts and computational procedures, computation practice including timed tests, and opplication of these skills in word problems.

The remediation approach at the LDC involves using multisensory teaching techniques in a very structured environment designed to remove the major obstacles to learning such as visual and auditory distractions. While students work in small groups of three, each student has an individualized curriculum to provide instruction in the areos where he demonstrates skill deficits. In addition to formal assessment of achieve-

ment and skill mastery, teachers use a test-teoch-test approoch to informally assess what a student has leorned ond to begin teaching ot a point appropriate for the individual student. Small units of information are presented sequentially and practiced until on automatic correct response can be given for three to five consecutive days. Due to memory deficits in many learning disabled students, overlearning appears to be necessary to ensure long-term retention.

Class time is structured to provide review of material recently learned through both oral and written drill, presentation of new moterial, aplication of new skills, and integration of new information with previously ocquired skills. Homework is assigned daily in each class to provide additional practice of skills leorned in class. Closses are designed to maximize opportunities for student response and success experiences. An incorrect answer given by a student is immediately corrected and reinforced so that the student is more likely to remember the correct response. Student-teacher interaction focuses on proise and positive reinforcement of correct answers or approximations of the correct response.

Additional Programs

In addition to the regular day program during the school year, the Center offers a study hall program two nights per week for students in grades five through twelve. Study Hall is held Monday and Wednesday evenings from 7:00 to 9:00 p.m. and is staffed by two members of the LDC faculty. The student/teacher ratio does not exceed five students per teacher. The program is intended to provide assistance in completing homework ossignments through orgonization of materials, drill and review, and instruction in study skills.

The LDC also offers a six-week Summer Program for three hours per day following the some instructional program as the oademic year. The Summer Program provides on opportunity for students already enrolled in the school program to continue instruction throughout the summer and therefore prevent the regression of skills that can occur without daily practice. The program is also intended to serve students who ore not enrolled in the school year program but who may benefit from on intensive remediation program during the summer before returning to their regular classrooms in the foll.

Aging and the Skin

Claude S. Burton, M.D., Peter Heald, M.D., and J. Lamar Callaway, M.D.

The heart wears out in a hundred years, the kidney lasts about 150. But the skin never wears out. Whoever heard of anyone dying of old skin? Skin is continually in the process of rejuvenation. Nevertheless, there are changes that occur to our skin that alter its appearance and performance. Wrinkles, thinning, changing pigment, and change in elasticity are commonly associated with aging. These are highly visible clues that reflect a more general process. The market for products to care for these changes is enormous. Billions are spent annually. A paradox exists in that most of the money is spent where the least benefit can be expected. Most of the products are applied after the damage is done. In this case an ounce of prevention is truly worth a pound of cure.

There is no preparation or formula known to reverse aging of the skin. Much of what we call aging is premature deterioration due to trauma from the sun. To illustrate this point we ask our patients to compare the "aged skin" on their hands and forearms to skin that is just as "old" in the axilla

or buttocks area. In these areas with little sun exposure patients are surprised to see how "youthful" their skin really looks. Unfortunately, though the convincing is easy there is little that can be done at this point to reverse the damage. Changes due to sun are cumulative and much of what we see in a person's skin at age 50 reflects sun exposure as a child.

There are many reasons other than vanity to protect our skin. The skin is a barrier against an otherwise hostile environment. Skin that is sun damaged doesn't lubricate normally and is subject to drying and cracking. This is the result of sun damage to the glandular elements in the skin and damage to the basal cells which replenish the epidermis. Sun damaged skin is thin, fragile, and heals poorly. The elastic substance in the tissues is exquisitely sensitive to ultraviolet and thermal radiation.

The solution should be obvious. We must protect our children from the early ravages of sunlight. With the use of common sense, and sunscreens, our children will have the chance of youthful skin all of their lives.

For adults, sunscreens are useful in preventing further damage and

should reduce the incidence of skin cancer. At this latitude daily application in the spring and summer should become a habit like brushing our teeth. Since damage is usually present, additional care is often needed. Aged skin lubricates poorly and will often require the topical application of a moisturizing agent and the avoidance of soap. Vitamin C supplementation in modest doses (1-2 g daily) is recommended to promote the integrity of the collagen in the skin. Collagen is the leather that makes up the bulk of skin. The thinning of skin with age is largely the result of diminished collagen. Vitamin C levels tend to be lower in elderly persons and in many cases are near the levels seen in scurvy! It is expected that Vitamin C will retard the thinning process and promote proper wound healing, and it may also improve the easy bruisability noted with age. Studies to confirm the usefulness of this recommendation are underway and preliminary results look promising. It is no longer true that nothing can be done about "aging."

From the Department of Medicine, Duke University Medical Center, Durham 27710.

4-Aminoquinolines Can Be Dangerous to Your Health: Chloroquine (Aralen) Intoxication

Ronald B. Mack, M.D.

WHAT in the name of Mithridates (Mithridates VI was a king, legends relate, who claimed he had discovered an antidote for every poisonous substance. Thus the archaic term "mithridatic" referring to an antidotal or protective mixture) are the 4-aminoquinolines? I asked some of our medical students and got such answers as: "Do they take unleaded gasoline?" "Four people who acquired AIDS from using the same comb." "An English rock group who recently sold a million records." These were the good answers.

During World War II (surely you remember the Big One) the antimalarial agent quinine was no longer available to the forces that were trying to overcome Hitler, Mussolini, Tojo and their minions. Quinine is the major alkaloid of cinchona bark (which is indigenous to certain areas of South America). Cinchona alkaloids were the only chemotherapeutic agents available for the specific therapy of malaria until the 1930s. In the third decade of this century quinacrine was introduced as an antimalarial agent. It soon became apparent that quinacrine was superior to quinine. Quinacrine was not an ideal drug, however, as it did not apparently act as a true prophylactic against malaria and did not cure benign tertian malaria. World War II provided a very strong impetus to develop an antimalarial that was a more effective and less toxic drug. By the time the war ended, chloroquine was developed and found to be a most promising chemical to combat malaria. Nevertheless millions of doses of quinacrine (Atabrine) were reluctantly ingested by Allied servicemen especially those serving in highly endemic malaria areas such as Africa and the South Pacific. (Will any of us ever forget the terribly bitter taste of Atabrine and the ugly yellow skin color that resulted from its use? Ugh!! It makes the food in the hospital cafeteria taste like Maxim's by comparison.)

So you might ask, why an article on chloroquine? Surely you don't see much malaria in North Carolina. Why is the author bothering us with war stories and a group of drugs that the average health care professional in our State does not need to know about? I submit to you that this group of drugs is being used in North Carolina and against some fairly common diseases at that. *Giardiasis* is probably the most common parasitic cause of diarrhea in America and is the most common cause of parasitic-induced malabsorption in this country. The treatment of *Giardiasis* is either quinacrine or metronidazole (Flagyl). *Rheumatoid arthritis*, *dis-*

coid lupus erythematosus, and *extraintestinal amebiasis* are other diseases for which chloroquine is utilized and certainly plenty of patients with these diseases exist in our fair State.

So what's the big deal here? Is chloroquine that toxic in overdose? You bet your bippy it is!! (I haven't been this excited since Margaret Thatcher showed her ankles in *People* magazine.) Chloroquine overdose kills, is commonly fatal in children, and the entire time course from ingestion to death can be short indeed. Many authors consider a single dose of 1.5 grams of chloroquine base to be toxic in an adult and a single dose of 2.0 grams to be potentially lethal. For children and adults, 35-50 mg/kg of chloroquine base may well be a fatal dose. Chloroquine phosphate USP is the name of this drug as you write it in a prescription but only 60% of it is the chloroquine base. The clinical features of an acute chloroquine poisoning episode are classically divided into three categories: *neurological*, *respiratory*, and *cardiovascular*.

Neurological adversities include drowsiness, often the earliest feature, photophobia, diplopia, and seizures. Seizures can be a presenting sign but are just as likely to be seen pre-terminally. *Respiratory* difficulties are quite common and variable but include quite rapid superficial breathing all the way up to and including sudden apnea and respiratory failure. As if these problems are not bad enough, the worst is yet to come: *cardiovascular manifestations* are awesome in chloroquine intoxication and most authorities submit that the acute toxic effects of chloroquine are mainly exerted on the heart. This drug is a powerful cardiotoxin; it reduces the excitability and conductivity of cardiac muscles similar to the effects observed with quinidine. The cardiovascular effects of chloroquine in overdose include vasodilatation and hypotension (a sudden fall in blood pressure is a very characteristic feature of this overdose), and of course arrhythmias and *cardiac arrest*. The quinidine-like EKG abnormalities include widened QRS, inverted or flattened T waves, and ventricular tachycardia. Myocardial toxicity and arrhythmias are probably the cause of death in chloroquine poisoning rather than vasomotor, respiratory, or neurologic insult.

Chloroquine is quite rapidly and almost completely absorbed from the GI tract. The drug is rapidly taken up by the tissues where it is deposited in quite significant amounts. Approximately 55% of chloroquine in the plasma

is bound to nondiffusible plasma constituents. According to autopsy data the concentration of chloroquine in the heart, liver, kidney, and lung greatly exceeds concentrations in the blood. Of interest is the fact that brain concentrations are similar to blood concentrations. The volume of distribution (V_D) of this drug is quite high. (Readers who like to think ahead will quickly surmise that because most of the drug is not in the blood the prospect of removing it via extracorporeal mechanisms is slim to none.)

It cannot be emphasized too strongly than an acute chloroquine ingestion is a "fire engine red" emergency first class. This is especially true when a child is involved. Time is not on your side here; death occurs within a few hours after ingestion of a toxic dose. Chloroquine phosphate (Aralen) is supplied in tablets containing 500 mg, 300 mg of which is the base. Thus a 2-year-old environmental investigator weighing 28 pounds (12.7 kg) needs to ingest only 2 such tablets to achieve mortality. Even the ingestion of 1 such tablet has been reported to cause death in an infant. Now that's frightening!! What are we really talking about here? — we are talking about a medicine used throughout our State for various diseases that has a narrow margin of safety between therapeutic and toxic doses, a rapid onset of an extremely toxic syndrome with fatal outcome not uncommonly, with no specific antidote or antagonist and death resulting in one to three hours due to cardiorespiratory failure.

The treatment of chloroquine overdose is, to say the least, meager. As stated previously there is no specific antidote to counteract the acute toxicity — no naloxone or methylene blue or BAL or such. Obviously gastric emptying, if performed early enough, could be life-saving. The drug is absorbed quite rapidly, as noted; therefore administration of syrup of ipecac in the home to children 1 year of age or above very very shortly after ingestion is the way to go. (Children less than 1 year of age are generally better off getting ipecac syrup in an emergency room where they can be monitored by professionals.) Gastric lavage can be implemented as an alternative if done as soon after ingestion as possible. If symptoms have already appeared by the time you see the patient, gastric emptying may be a futile gesture. If the patient ingested the chloroquine on a "full" stomach, i.e., after a meal, the drug's absorption is slowed considerably and gastric emptying is surely indicated. After gastric emptying has been accomplished, administration of activated charcoal and a saline cathartic

might decrease the prospect of further chloroquine absorption. Of course you must support respiration. The other complications are treated in a supportive fashion — using vasopressors to counteract hypotension, diazepam for seizures, a ventilator, a cardiac pacemaker, and so on. Some of the literature, including recent articles, talk about the use of urine acidification to increase the renal excretion of chloroquine. However, in my opinion, the data are soft and this method cannot be endorsed with the limited data that are available.

Quinacrine (Atabrine) is a drug similar to chloroquine (an acridine compound consisting of a substituted 4-aminoquinoline radical linked to a benzene ring) and can cause nausea, vomiting, and diarrhea when taken in overdose, and when consumed in large overdose can cause a cardiac death similar to chloroquine. Because of the increase in the discovery of patients with giardiasis (especially children), more and more of this medication will be available to preschool taste experimenters. Beware also of patients with glucose-6-phosphate dehydrogenase-deficiency who receive quinacrine — this combination can result in acute hemolysis. Atabrine, even in therapeutic dosage for giardiasis, commonly causes patients to acquire a very yellow hue to their skin. This yellow pigment is concentrated in the epidermis in concentrations 100-200 times that of plasma. A recent paper¹ recommends examining the patient's palms, fingernails, and urine with a Wood's lamp. If the patient has been ingesting quinacrine these areas emit a brilliant yellow green fluorescence, and the Wood's lamp helps you to distinguish this cause from other diseases including congenital cowardice.

This group of drugs is particularly scary to me and I hope to the reader. I have resolved not to get malaria or giardiasis or rheumatoid arthritis or discoid lupus or any such craziness. The way to achieve this, I am convinced, is to try the Mack Diet which in my opinion is superior to the Pritikin Diet, Weight-Watchers, Cambridge Diet, Slim Fast Diet to name a few. The diet is simple and easy to prepare — pasta in any form at least twice a day. No disease could possibly attack you after you have been on this diet for a while; there would be no place for the illness to land. I am convinced that spaghetti is anti-inflammatory.

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Moonlighting: A Practice to be Encouraged?

William S. Kelly, M.D. and Penny C. Sharp, B.S.

RESIDENTS who moonlight, i.e., engage in extramural professional activity, are almost universally enthusiastic about its value as an educational experience. Moonlighting is officially discouraged by the Liaison Committee on Graduate Medical Education (LCGME) of the Association of American Medical Colleges, however, as a practice that is "inconsistent with the educational objectives of house officer training."¹ In fact, many institutions do permit residents to moonlight, and faculty members and residency directors are sometimes heard to grudgingly admit that some of their best residents do moonlight. Perhaps the controversy exists because there is virtually no literature that documents what residents do while moonlighting. We present data that document the moonlighting experience of a second year family medicine resident and compare that experience with the residency-based outpatient experience during the same time interval.

Several studies have defined the content of family medicine both in academic and in private practice settings.²⁻⁴ Some interesting differences in the academic and private practice of family medicine have been demonstrated. It seemed likely that there would be marked differences between the patient populations seen while moonlighting and while performing residency-based outpatient medicine even though much of the moonlighting was done in a private family practice setting.

The sample consists of 687 patient encounters. Any given patient may have been seen more than once and may have had more than one diagnosis. Of these, 282 encounters took place in the Family Practice Center of the family medicine residency program of the Bowman Gray School of Medicine at North Carolina Baptist Hospital during the period from July 1, 1982 to December 31, 1982. These patients were seen both as scheduled appointments during regular clinic hours and after hours while on call. Four hundred and five patient encounters occurred while moonlighting during the same period: 119 patients were seen in the emergency departments of three small community hospitals near Winston-Salem; the remaining 286 moonlighting patients were seen in a "franchised" fee-for-service private family medicine practice in Winston-Salem. The clinical impressions at the time of the encounter were recorded for all patients seen in the Family Practice Center, whether during regular clinic hours or in after hours "emergency" clinic visits. Similarly, the clinical impressions, together with the age, sex and race of the patient, were recorded for all patient encounters while moonlighting.

The clinical impressions were coded using the International Classification of Diseases, 9th revision (ICD-CM9).⁵ The diagnoses of the patients seen in the Family Practice Center were coded by the North Carolina Baptist Hospital Medical Records department. The diagnoses of patients seen while moonlighting were coded by the authors. The diagnoses were grouped into the 18 major diagnostic categories of the ICD-CM9 to allow easier comparisons.

The data are presented in table 1. In several categories there are very marked differences in the percentages of patients seen while moonlighting compared with the residency-based outpatient experience. For example category 3 (which includes diabetes), category 5 (which includes depression and anxiety states), category 7 (which includes hypertension), category 11 (which includes normal pregnancy), and category 18 (which includes routine adult and well-child exams) were all more common in the Family Practice Center than in the moonlighting encounters. On the other hand category 8 (which includes upper respiratory infection) and category 17 (which includes lacerations and sprains) were much more common in the moonlighting encounters.

The differences in the patient populations seen in the Family Practice Center as opposed to moonlighting can perhaps be more easily seen in table 2 which lists the top 10 diagnoses ranked by frequency for the Family Practice Center and moonlighting data. Only acute upper respiratory infection and urinary tract infection appear on both lists.

Discussion

Moonlighting more than doubled the number of outpatient encounters in the six month period in question and provided significantly more exposure to urgent and emergency patient problems. This results in part from the fact that second year residents are only in the Family Practice Center an average of 10 half days per month and that few patients, a maximum of 10, were seen in any half-day clinic. The result is that a resident's schedule quickly fills with patients with chronic diseases, such as hypertension and diabetes mellitus, and with patients for routine care, such as health maintenance examinations and well baby check-ups, leaving little time for patients with urgent and emergency problems. The data demonstrate that moonlighting provides significantly more exposure to patients and to a wider range of patient problems than would normally be seen by second year residents at least in this particular family medicine residency program. In addition, moonlighting gives the resident significantly more experience in handling urgent and emergency medical problems.

From the Department of Family and Community Medicine, Bowman Gray School of Medicine, Winston-Salem 27103.

Table 1

Number and Percent of Diagnoses by Diagnostic Category for Residency Based and Moonlighting Patient Encounters

Diagnostic Category	Residency Based		Moonlighting	
	Number	Percent	Number	Percent
1. Infectious & parasitic diseases	25	7.9	23	5.0
2. Neoplasms	2	.6	2	0.4
3. Endocrine, nutritional & metabolic dis., immunity disorders	25	7.9	6	1.3
4. Dis. of blood and blood-forming organs	1	.3	1	0.2
5. Mental disorders	22	6.9	18	3.9
6. Dis. of nervous system & sense organs	10	3.2	39	8.6
7. Dis. of circulatory system	29	9.1	21	4.6
8. Dis. of respiratory system	47	14.8	102	22.4
9. Dis. of digestive system	6	1.9	16	3.5
10. Dis. of genito-urinary system	21	6.6	38	8.3
11. Pregnancy, childbirth & puerperium	21	6.6	2	0.4
12. Dis. of skin & subcutaneous tissue	9	2.8	22	4.8
13. Dis. of musculoskeletal & connective tissue	19	6.0	20	4.4
14. Congenital anomalies	—	—	1	0.2
15. Conditions originating in perinatal period	—	—	—	—
16. Symptoms, signs & ill-defined conditions	31	9.8	22	4.8
17. Accidents, injury, poisoning & violence	8	2.5	112	24.6
18. Supplementary classification (Preventive medicine, family planning, education, etc.)	41	12.9	11	2.4
	317	99.8	456	99.8

There is, of course, the very tangible benefit of extra income for residents who moonlight, but that is not relevant to this discussion. There is also an aspect of moonlighting that cannot be quantified, the feeling of being fully responsible for the patient. Nothing promotes more care with the history and physical examination and more thorough consideration of diagnostic and therapeutic options than that sense of total responsibility.

It appears that moonlighting is not a practice to be discouraged but one that should be encouraged as long as it does not interfere with the resident's performance in his residency program. Several steps could be undertaken to make moonlighting a better educational experience and to better safeguard patients seen by moonlighting residents. These entail better availability of the back-up doctors,

follow-up on official interpretation of relevant studies such as x-rays and electrocardiograms, and timely chart review by the back-up attending or other physician with residents being made aware of any errors in diagnosis or treatment.

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Table 2

Top Ten Diagnoses Ranked by Frequency for Residency Based and Moonlighting Patient Encounters

Rank	Residency Based		Rank	Moonlighting	
	Number	Percent		Number	Percent
1. Hypertension	21	6.8	1. Acute Upper Respiratory Infection	32	6.5
2. Diabetes Mellitus	19	6.2	2. Open Wound	28	5.7
3. Routine Medical Exam — Adult	18	5.9	3. Tonsillitis, Pharyngitis	29	6.4
4. Normal Pregnancy	13	4.2	4. Bronchitis	21	4.3
5. Depressive Disorder	11	3.6	5. Otitis Media	16	3.5
6. Acute Upper Respiratory Infection	10	3.3	6. Sprains	16	3.5
7. Anxiety State	9	2.9	7. Urinary Tract Infection	15	3.0
8. Urinary Tract Infection	8	2.6	8. Sinusitis	15	3.0
9. Routine Child Health Exam	8	2.6	9. Motor Vehicle Accident	14	2.8
10. Abdominal Pain	7	2.3	10. Tinnitus	9	1.8
		40.4			40.5

"Superdoc!"

THE North Carolina Medical Society's Midwinter Conference for 1984 — "Superdoc!" — took place at the Holiday Inn Four Seasons Convention Center in Greensboro on January 27. There were 250 attendees including physicians, Auxilians, office managers and other staff members from physicians' offices across the state. Three speakers addressed the conference on three separate aspects of managing a medical practice.

Mr. Robert C. Runde, President of RCR Associates in Charlotte, gave attendees a step-by-step guide to computerizing a physician's office, touching on advantages and disadvantages of owning your own computer versus time sharing on mini-, micro-, and mainframe computers. He discussed when to consider computerizing and which office tasks most lend themselves to computerization. Many of those in attendance had specific questions for Mr. Runde about software packages, computer systems, and interacting with third-party payors via computers. While responding to the questions, he readily acknowledged that not all medical offices need to be computerized, and he warned of various pitfalls for offices that are.

Dr. Joseph L. Price, a physician in family medicine in Philadelphia, addressed the conference on two subjects: computerized medical records as a tool for patient management, and continuing medical education in the next decade. Dr. Price, who has designed his own program for medical offices, spoke about how to use the computer to generate possible diagnoses for specific patient complaints, to check



Dr. Joseph L. Price



Mrs. Helen Boyette, an auxiliary member from Chinquapin, was among the attendees who raised questions for each of the three speakers.



Mr. Robert C. Runde



Mr. Leif C. Beck

for possible drug-drug or drug-food interactions, to flag abnormal results for further attention while discussing treatment with a patient or a patient with a consulting physician. He stressed the time-saving feature of streamlining patient management by using the computer in the office. Dr. Price also talked about applying modern technology to continuing medical education programs by using clinical simulation models on small computers or interactive video disk presentations.

Mr. Leif C. Beck, chairman of a medical consulting firm, offered attendees useful tips on personnel management, money management, and practice marketing. As both an attorney and a tax expert, Mr. Beck was able to talk knowledgeably about compensation policies in medical offices, when and why to pay into retirement accounts, how to calculate collection ratios. He ended the conference with a consideration of practice marketing and how important it is to physicians, not only in terms of public relations but also from the perspective of market analysis for a new single or multi-physician office.

The conference closed with a wine and cheese reception, co-sponsored by the NCMS and the Guilford County Medical Society.

A Curious, Interested Doctor at Peace with the Complexities of Biology

Eugene A. Stead, Jr., M.D.

I enjoyed reading Drew's account of the principles of drug monitoring.

Molecular change at the site of action of a drug is the final culmination of a series of distribution curves, each with a wide base. I remember the excitement when the purified glycosides of digitalis leaf became available. One distribution curve, namely the amount of active agent in each pill, was narrowed. Because of the differences in preparation of the pills, the amount of drug available for absorption varied widely. The distribution curves of bioavailability have a broad base and purification of the glycoside was of little help until the base of this curve was narrowed by better formulation by the pharmaceutical industry.

We then ran into a new set of distribution curves. The rate of disappearance from the blood and the degree of attachment of the active drug to cell membranes and cellular structures showed wide variability. The desired hemodynamic effects were not readily predicted by the serum levels. Drew states some of the reasons for this. Digitalis levels do allow us to identify our noncompliant patients and the patients who have a level that produces toxicity in the majority of patients. This is, of course, progress.

We know that a series of distribution curves determine the way the kidney excretes the drug. We know that the free level of the drug is altered by many other drugs. There must be at least 50 more distribution curves to be mastered before we can accurately define in quantitative terms the effects of digitalis.

Students of all types come to us to learn the science of

clinical medicine. To me scientific medicine is a situation in which the doctor can control all the variables, elect a course and, after an absence of a number of days, return to find that the patient has stayed on the course charted by the doctor. Because of the complexity of biology with its thousands of overlapping distribution curves, this is rarely possible. I would rather have a doctor who continually observes the patient's course, knowing the depths of his ignorance, than a doctor who looks on himself as a scientist capable of controlling all the variables. An alert, curious, interested doctor who is at peace with the complexity of biology is a great asset to patients.

Kenneth Melmon,¹ a distinguished clinical pharmacologist, makes the same point in a paper entitled "Will the Sighted Physician See?"

"If we behave inappropriately we will continually press for miracle agents that do only good. Yet, in demanding substantial efficacy we are *asking* for chemical agents that intervene substantially in biological processes. Such agents used thoughtlessly or wrongly will produce disease. If we fail to think through this problem we will miss out on one of the biggest and most exciting challenges of medicine. That challenge is to observe the unexpected, to analyze it in the light of our knowledge and determine if we are truly seeing something new. It is the physician's privilege to observe biology in man, a model never fully replicated by laboratory animals."

Reference

1. Melmon KL: Will the sighted physician see? *The Pharos* 1984;47:2-6.

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(BRIEF SUMMARY)

DESCRIPTION

Each tablet contains 200 mg meprobamate and 325 mg aspirin.

INDICATIONS

Adjunct in short-term treatment of pain accompanied by tension and/or anxiety in patients with musculoskeletal disorders. Clinical trials demonstrated that in these situations relief of pain is somewhat greater than with aspirin alone. Effectiveness in long-term use (i.e., over 4 months) has not been assessed by systematic clinical studies. Physicians should periodically reassess usefulness of drug for individual patients.

CONTRAINDICATIONS

ASPIRIN: Allergic or idiosyncratic reactions to aspirin or related compounds.

MEPROBAMATE: Acute intermittent porphyria, allergic or idiosyncratic reactions to meprobamate or related compounds (e.g., carisoprodol, mebutamate, or carbomal).

WARNINGS

ASPIRIN: Use salicylates with extreme caution in patients with peptic ulcer, asthma, coagulation abnormalities, hypoprothrombemia, vitamin K deficiency, or those on anticoagulants. In rare instances, aspirin in persons allergic to salicylates may result in life-threatening allergic episodes.

MEPROBAMATE DRUG DEPENDENCE

Physical and psychological dependence and abuse have occurred. Chronic intoxication from prolonged ingestion of, usually greater than recommended doses, is manifested by ataxia, blurred vision, and vertigo. Therefore, carefully supervise dose and amounts prescribed and avoid prolonged use, especially in alcoholics and others with known propensity for taking excessive quantities of drugs. Sudden withdrawal after prolonged and excessive use may precipitate recurrence of preexisting symptoms.

ptoms, e.g., anxiety, anorexia, or insomnia, or withdrawal reactions, e.g., vomiting, ataxia, tremors, muscle twitching, confusion, states, hallucinations, and rarely convulsive seizures. Such seizures are more likely in persons with CNS damage or preexisting or latent convulsive disorders. Onset of withdrawal symptoms occurs usually within 12 to 48 hours after discontinuation; symptoms usually cease within next 12 to 48 hours. When excessive dosage has continued for weeks or months, reduce dosage gradually over 1 to 2 weeks rather than stop abruptly. Alternatively, a short-acting barbiturate may be substituted; then gradually withdraw.

POTENTIALLY HAZARDOUS TASKS: Warn patients meprobamate may impair mental or physical abilities required for potentially hazardous tasks, e.g., driving or operating machinery.

ADDITIVE EFFECTS: Since CNS suppressant effects of meprobamate and alcohol or meprobamate and other psychotropic drugs may be additive, exercise caution with patients taking more than one of these agents simultaneously.

USAGE IN PREGNANCY AND LACTATION

An increased risk of congenital malformations associated with minor tranquilizers (meprobamate, chloralhydrate, and diazepam) during first trimester of pregnancy, has been suggested in several studies. Because use of these drugs is rarely a matter of choice, their use during this period should almost always be avoided. The possibility that a woman of child-bearing potential may be pregnant at time of institution of therapy should be considered. Advise patients if they become pregnant during therapy or intend to become pregnant to communicate with their physicians about desirability of discontinuing the drug.

Meprobamate passes the placental barrier; it is present both in umbilical-cord blood at or near maternal plasma levels and in breast milk of lactating mothers at concentrations two to four times that of maternal plasma. When use of meprobamate is contemplated in breastfeeding patients, consider the drug a higher concentration in

breast milk as compared to maternal plasma levels.

USAGE IN CHILDREN: Keep preparations with aspirin out of reach of children. Equagesic® (meprobamate with aspirin) is not recommended for patients 12 years of age and under.

PRECAUTIONS

ASPIRIN: Salicylates antagonize uncoupling activity of probenecid and sulfinpyrazone. Salicylates are reported to enhance hypoglycemic effect of sulfonylurea antidiabetics.

MEPROBAMATE: Use lowest effective dose, particularly in elderly and/or debilitated, to preclude over-sedation. Meprobamate is metabolized in the liver and excreted by the kidney; to avoid excess accumulation exercise caution in its use in patients with compromised liver or kidney function. Meprobamate occasionally may precipitate seizures in epileptic patients. It should be prescribed cautiously and in small quantities to patients with suicidal tendencies.

ADVERSE REACTIONS

ASPIRIN: May cause epigastric discomfort, nausea, and vomiting. Hypersensitivity reactions, including urticaria, angioneurotic edema, purpura, asthma, and anaphylaxis may rarely occur. Patients receiving large doses of salicylates may develop tinnitus.

MEPROBAMATE: CNS Drowsiness, ataxia, dizziness, blurred vision, headache, vertigo, weakness, paresthesias, impairment of visual accommodation, euphoria, overstimulation, paradoxical excitement, fast EEG activity.

GI: Nausea, vomiting, diarrhea. **CARDIOVASCULAR:** Palpitation, tachycardia, various forms of arrhythmia, transient ECG changes, syncope, hypotensive crisis.

ALLERGIC OR IDIOSYNCRATIC: Milder reactions are characterized by itchy urticaria, or erythematous maculopapular rash, generalized or confined to the groin. Other reactions include: leukopenia, acute nonthrombocytopenic purpura, petechiae, ecchymoses, eosinophilia, peripheral edema, adenopathy, fever, fixed drug eruption with cross-reaction to carisoprodol, and cross-sensitivity between meprobamate, midbamate and mepramate. **Rare:** more severe hypersensitivity

reactions include: hyperpyrexia, chills, angioneurotic edema, bronchospasm, oliguria, and anuria. Also, anaphylaxis, exfoliative dermatitis, stomatitis, and proctitis. Stevens-Johnson syndrome and bulous dermatitis have occurred.

HEMATOLOGIC (SEE ALSO "ALLERGIC OR IDIOSYNCRATIC"): Agranulocytosis, aplastic anemia have been reported, although no causal relationship has been established and thrombocytopenic purpura.

OTHER: Exacerbation of porphyric symptoms. **DOSEAGE AND ADMINISTRATION:** Usual dose is one or two tablets, 3 to 4 times daily as needed for relief of pain when tension or anxiety is present. Not recommended for patients 12 years of age and under.

OVERDOSSAGE

Treatment is essentially symptomatic and supportive. Any drug remaining in the stomach should be removed. Induction of vomiting or gastric lavage may be indicated. Activated charcoal may reduce absorption of both aspirin and meprobamate. Aspirin overdose produces usual symptoms and signs of salicylate intoxication. Observation and treatment should include management of hyperthermia, specific parenteral electrolyte therapy for ketoacidosis and dehydration, watching for evidence of hemorrhagic manifestations due to hypoprothrombemia which, if it occurs, usually requires whole-blood transfusions. Successful attempts with meprobamate have resulted in drowsiness, lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse. Some suicidal attempts have been fatal. The following data, reported in the literature and from other sources, are not expected to correlate with each case (considering factors such as individual susceptibility and length of time from ingestion to treatment), but represent usual ranges reported. Acute simple overdose (meprobamate alone). Death has been reported with ingestion of as little as 12 grams meprobamate and survival with as much as 40 grams.

BLOOD LEVELS: 0.5-2.0 mg percent represents usual blood-level range of meprobamate after the apoc

does. The level may occasionally be as high as 3.0 mg percent.

3-10 mg percent usually corresponds to findings of mild-to-moderate symptoms of overdose, such as stupor or light coma. 10-20 mg percent usually corresponds to deeper coma, requiring more intensive treatment. Some fatalities occur.

At levels greater than 20 mg percent, more fatalities than survival can be expected. Acute combined overdose (meprobamate with other psychotropic drugs or alcohol). Since effects can be additive, history of ingestion of a low dose of meprobamate plus any of these compounds (or of a relatively low blood or tissue level) cannot be used as a prognostic indicator.

In cases of excessive doses, sleep ensues rapidly and blood pressure, pulse, and respiratory rates are reduced to basal levels. Any drug remaining in stomach should be removed and symptomatic treatment given. Should respiration or blood pressure become compromised, respiratory assistance (CNS stimulants, and pressor agents should be administered cautiously as indicated). Diuresis, osmotic (mannitol) diuresis, peritoneal dialysis, and hemodialysis have been used successfully in removing both aspirin and meprobamate. Alkalinization of the urine increases excretion of salicylates. Careful monitoring of urinary output is necessary and caution should be taken to avoid overhydration. Relapse and death, after initial recovery have been attributed to incomplete gastric emptying and delayed absorption.

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Secondary Syphilis Masquerading as AIDS in a Young Gay Male

Raymond A. Smego, Jr., M.D., Randall W. Moreadith, Ph.D., Paul C. Kleist, M.D., and Donald L. Granger, M.D.

THIS is the story of our learning experience with a 38-year-old white male homosexual who was admitted to Duke University Medical Center with complaints of headache, fever, skin rash, and weight loss. His symptoms began six weeks earlier with the onset of vague low back pain and persistent temporal-occipital headaches that were partially relieved by salicylates. He also noted diffuse myalgias, generalized lymph gland enlargement, and night sweats which soaked his bedsheets. He had nausea and vomiting, anorexia, 3-5 non-bloody stools per day, and a 20-pound weight loss. Three discrete, non-pruritic erythematous macules had appeared over the ulnar eminence of his left palm and progressed over three weeks to become small papules with superficial scaling and crusting. There was no purulent discharge or bleeding from the lesions. Other lesions arose on the upper and lower extremities, abdomen, back, and face which were mildly tender to touch. The patient recorded intermittent temperatures to 102°F with rigors over this 6-week period.

At age 24 the patient had moved to New York City where he lived for 10 years. He admitted to having greater than 5,000 homosexual partners over the past 16 years, engaging in both active and passive anal-genital and oral-genital intercourse. He had been treated numerous times for gonorrhea. There was a history of oral and parenteral drug abuse in the distant past but none in the 10 years prior to admission. He moved to North Carolina in 1981 and claimed to have had an exclusive sexual relationship with a single male partner since that time.

There was an acniform rash on his face, neck, and trunk. There were several crusted, healing papular lesions on the left palm. Multiple erythematous macular and papular lesions, which appeared to be at different stages of development, were present on both lower extremities below the knees; several of these were slightly raised and had a distinct violaceous hue, and a similarly colored subungual lesion of the left great toe was present. There was generalized non-tender lymphadenopathy involving occipital, posterior and anterior cervical, supraclavicular, axillary, epitrochlear, and inguinal node groups. The liver was enlarged with a tender palpable edge; the spleen was not felt. Pertinent laboratory data included a WBC count of 5500/mm³ with 54% polymorphonuclear cells, 35% lymphocytes, and 11% monocytes. The erythrocyte sedimentation rate was 52 mm/hr. A roentgenogram of the chest was

normal. Lumbar puncture performed because of persistent headache revealed 2 lymphocytes/mm³ with normal glucose and protein concentrations and a negative India ink exam. The serum VDRL was reactive at a dilution of 1:64; the cerebrospinal fluid VDRL was non-reactive. A serum fluorescent treponemal antibody-absorption (FTA-abs) test was positive. Serologic tests for *Toxoplasma gondii* showed an indirect hemagglutination titer of 1:64, and IgG and IgM antibody titers of less than 1:16 and 1:8, respectively. Hepatitis B surface antigen was negative but anti-HBs and anti-HBe antibodies were present; IgG antibodies to hepatitis A were also detectable. Serum protein electrophoresis showed hypoalbuminemia with a slight increase in gamma globulin concentration.

We felt that the patient was at a high risk for AIDS¹ and placed him on blood and enteric precautions. Biopsies of three geographically and morphologically distinct skin lesions revealed no evidence of Kaposi's sarcoma. They showed vasculitis with perivascular round cell infiltrates compatible with the histologic changes of secondary syphilis. Darkfield examination was attempted but no exudate could be expressed from multiple dry lesions. The patient was given benzathine penicillin G 1.2 million units intramuscularly in each buttock. Eight hours later he complained of slight nausea and developed a fever of 101.6°F which subsided spontaneously. Over the next 48 hours there was a significant decrease in the rash over his lower extremities and palm, and he was subjectively improved. He was discharged on the seventh hospital day. When contacted two months later, he reported a complete resolution of the skin lesions. He felt well and was gaining weight. He still had swollen lymph nodes in his neck but these were diminished in size since discharge.

Comment

The clinical features of secondary syphilis are protean, with constitutional, mucocutaneous, and parenchymal manifestations, and accordingly over the years the disease has been applauded as the "great imitator." A variety of morphologic skin lesions are the most commonly recognized physical findings, including macules, maculopapules, papulosquamous scales, pustules, and variations thereof. All stages may be present at one time and become widely distributed to the trunk and extremities. Location of lesions on the palms and soles strongly suggests the diagnosis. These lesions typically appear 2-10 weeks after the primary infection, last about 4-8 weeks and then resolve spontaneously. Constitutional symptoms such as malaise,

From the Department of Medicine, Duke University Medical Center, Durham 27710.

anorexia, weight loss, arthralgias, and low-grade fever may occur in about 70% of cases. Highly infectious mucous patches, ulcers, and condyloma lata involving oral and genital mucus membranes, and painless generalized lymphadenopathy are also frequently seen. Less commonly, visceral involvement especially of the central nervous system can arise from seeding during spirochetemia.

In this gay male the combination of constitutional complaints, diffuse lymph node enlargement, and widespread skin lesions was mistakenly attributed to AIDS by both the patient and the medical staff upon admission. Indeed, many of these features were compatible with either the AIDS-related complex¹ which may represent a prodrome to the development of full-blown AIDS, or with disseminated Kaposi's sarcoma.¹

Histologic sections of multiple skin biopsy specimens revealed no evidence of Kaposi's sarcoma but demonstrated small-vessel vasculitis with perivascular mononuclear cell infiltration. These findings are consistent with the obliterative endarteritis produced by *T. pallidum*.

The diagnosis of secondary syphilis can be made serologically with demonstration of a reactive non-treponemal reaginic test such as the VDRL, plus a positive fluorescent treponemal antibody-absorption (FTA-abs) test. Quantitative VDRL titers greater than 1:16 indicate active, untreated

infection. Darkfield examination of serous exudate from moist lesions of secondary syphilis with visualization of spirochetes will also establish the diagnosis. *T. pallidum* can at times be demonstrated from dry lesions and lymph nodes by saline aspiration.

A compatible clinical picture and serologic evidence of active infection strongly suggested a diagnosis of secondary syphilis in this patient. The therapeutic response to benzathine penicillin G, manifested by defervescence, an increase in the patient's sense of well-being, clearing of all skin lesions, and a reduction of lymph node size within one week further supported this impression. Such a response would have been inconsistent with a diagnosis of AIDS.

Secondary syphilis masqueraded as AIDS in this patient. When caring for sexually active gay males, common sexually transmissible diseases such as syphilis should be strongly considered and excluded. Serologic testing for *T. pallidum* should be performed on these patients, especially if skin lesions, adenopathy, and systemic complaints are present. Darkfield microscopy may further aid in diagnosis.

Reference

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Medical Memories — Tattoos: The Last Short Arm Inspection Conducted by the Army

John H. Felts, M.D.

A neurosurgical friend recently passed along a fascinating review of tattooing (Fried RI: The psychodynamics of tattooing: a review. *Cleve Clin Q* 1983;50:239-242), which recalled my own military adventures with the tattooed. One came during my internship more than three decades ago. The neurosurgical ward in those years at Walter Reed Army Hospital always had a few young paraplegic or quadriplegic patients, often paratroopers, whose spinal cord injuries had resulted not only from martial deeds but also from motorcycle accidents. We also had to care for a number of comatose young soldiers who had sustained head injuries in such accidents.

In my own personal diagnostic and prognostic classification, some patients were considered to have either motorcycle syndrome I or motorcycle syndrome II. Those with Type I had suffered spinal cord injury and were in varying stages of recovery and rehabilitation, while those in Group II were unconscious because of head injuries. Obviously, the prognosis was worse for those in the second category, although many quadriplegic patients also had rather dim prospects.

Almost all shared a few signs, partly attributable to their search for identity during the rite of adolescent passage, and partly to the catabolic stress of injury. They were tattooed, often elaborately, bearing such classical motifs as "Remember the Maine," patriotic phrases ("God, Country and Mother"), and phallic words and symbols — snakes, naked women who would wiggle when the deltoid was flexed, and the like. These decorative assertions of manhood were ironically negated by signs of negative nitrogen balance and feminization — gynecomastia, female pubic hair escutcheon, and soft testes. The very necessary acts of assertive masculinity, performed by gladiators on two-wheeled stallions as they flaunted their independence by shunning helmets, had led to their sexual neutralization with only tattoos left as dermal memorials.

Several years later, while serving in Europe with an infantry regiment, I again was faced with the need for considering the tattoo. Our division was scattered north of Frankfurt at posts along the Limes, the same line that marked the northern frontier of Caesar's legions when they had occupied Germany. The Romans had recognized that

invasion from the east was most likely through the Fulda gap a few miles to the north and had deployed their forces accordingly. Our armies had, sensibly enough, been arrayed along the same line, again concerned about invasion from the east. The East German border was very near and our maneuvers were through parts of Hesse which soon became as familiar to us as they had to Caesar's legions. While I was there, archeologists, excavating within the walls of the caserne housing our 8th regiment in Butzbach, had unearthed artifacts of Caesar's 8th Nubian legion which had occupied the same site.

Away from home in a country recovering from a terrible war, it was hardly surprising to find venereal disease virtually epidemic. Despite their vigorous, well-coordinated efforts, American and West German venereal disease control personnel could do little but try to be sure that penicillin was appropriately dispensed. Catching the clap (also known as gleet, strain, rupture or running reins) under such circumstances may have been as symbolic of negotiating adolescence and defying authority as being tattooed.

My regimental commander at the time was authoritarian, something of a moralist, and given to deep thought. Well indoctrinated as to the importance of guarding the Fulda gap and extremely conscious of Russians just across the border, he concluded he must do more to protect our troops from spirochetes and gram negative cocci. Relying on sources unknown to the rest of us, he discovered that our potential enemies to the east were arranging for prostitutes to be infected and sending them in droves across the border on "sex patrols" to seek out "our boys," and lay them low with deadly germs. He further determined that "Pachucos," Hispanic delinquents in the Army, were somehow responsible for the passage of the infected from one Germany to the other and thus for the high VD rate among our troops. Something therefore had to be done to control the pox.

I was summoned to his office on a gray, cold, winter's day some 30 years ago and directed to devise measures to assure that members of our regiment would not be victims of such a plague. He also suggested that identification of Pachucos among us would help him to learn more about their operations in U.S. Army Europe. Trained only in how to seek out subversion of individuals by disease, I hardly knew how to think about the Colonel's revelations, much less approach them therapeutically and diagnostically.

Fortunately I remembered from earlier Army days as an

From the Department of Medicine, Bowman Gray School of Medicine, Winston-Salem 27103.

enlisted man the payday parade known as Short Arm Inspection in which we marched in single file to qualify for our \$21.00 a month. Wearing only our raincoats and boots, each of us before approaching the pay table faced an appreciative inspector, opened our raincoats and stripped our urethras. If no discharge was forthcoming, we were given our money and allowed to get dressed. Before going to town, however, we had to sign out and pocket a prophylactic containing mercury to combat Venus in the event we encountered her.

Pachucos identified themselves by a tattoo in the webbing between the thumb and index finger so that conspirators could be discovered at Short Arm if stripping were carried out twice, right-handed and left-handed, with the dorsum of the hand in front. Although by that time enlisted men no longer had to prove virtue every payday, the option to carry out an inspection as a health measure was retained, allowing us to inspect our troops for their own good when we thought it necessary. Each officer in our medical company was therefore assigned a corpsman and a battalion to inspect.

We roused our suspects in the early hours of the morning, described the proper procedure — raincoats, boots, single-file and manual techniques — and carried out our investigations. Several cases of urethritis were discovered, several men were AWOL and a few bearers of the terrible tattoo were found and reported to our Colonel. A few more turned out to have marked themselves with ink only, perhaps aspiring to participate in the nefarious doings of their role models. For them soap and water conferred inno-

cence.

We never learned what happened to those truly tattooed, although our Colonel was certainly pleased when we reported our findings. Perhaps our data were ignored; at least the VD rate did not fall. Our Colonel might have felt that his efforts were insufficiently appreciated. At any rate, shortly after our pre-dawn reconnaissance, he completed his tour of duty and returned to the States.

His successor, more avuncular and less bedeviled, took a different approach. Rather than emphasize the problem, he instructed us not to report cases of gonorrhea, just to treat the infected. This order simplified my administrative life because we had to submit monthly venereal disease reports, in code lest our putative enemies learn of the sad medical and moral plight of our occupying army. My responsibilities included signing the report after it was encoded, but I had not yet been cleared by security to look at the coded report, which, of course, I could not decipher.

To cope with problems of morale our division had a Character Guidance Council with representatives from each detachment. We met monthly at division headquarters to derive the morality index for the past 30 days. This was done by plotting chapel attendance rate against VD rate. The council and the division commander were gratified at the improvement in morale and morality that the new commander had brought to our regiment. He and I were each proud to have contributed to such an achievement. I was also pleased that I may have directed the last nocturnal Short Arm Inspection in the history of the United States Army.

A Suggestion for Decreasing the Number of Medical Publications

DR. SKENE, in his characteristically able inaugural address at the last meeting of the American Gynecological Society, stated that during the past eight years, 804 books and 7505 journal articles and pamphlets had been added to the literature of gynecology. An inference may be drawn from this of the increase of medical literature in general. The question naturally arises whether this *embarras des richesses* is an unquestionable gain. It indicates, it is true, a wonderful diffusion of printed matter among a limited number of individuals, constituting one of "the learned professions," who, as a rule, lead exceptionally busy and useful lives. This being the case, they have a right to demand of those who purvey to their intellectual wants material which shall be digestible, assimilable, and calculated to insure healthy growth.

A survey leads us to the conclusion that the multiplication of journals has been entirely out of proportion to the demands of the profession, and that the majority of them, like too many of our younger institutions of learning in this country, are leading anything but a vigorous existence, their chief object being, apparently, to satisfy the ambition, of those concerned in their projection. Herein lies a grand indication for reform. Not that we desire to have *less* literature diffused, but *better*. This can be accomplished in several ways. One is concentration; the value of which is apparent enough, if one will but recall the most successful agencies around us for the advancement of knowledge, charity, or commerce. Another, is a more rigid censorship. With two hundred and more hungry editors, eager to grasp at anything which is offered, anything to fill their columns, no matter how immature, how unskillfully arranged, or

how inconclusive, what wonder is it that complaints are constantly made of the valuelessness of a very large portion of the current medical literature? It is as ephemeral as the mist before the rising sun. Very aptly does Dr. Skene remark in the address to which allusion has been made, "this multitude of gentlemen, who write more than they read, 'scatter like deer at the sound of the hunter's horn' when compelled to defend themselves in public discussion before a tribunal of competent judges in well-regulated medical societies."

Another means by which the overproduction in medical literature may be checked, is by making the terms between author and publisher analogous to those which obtain in all ordinary business enterprises, a *quid pro quo*. The inducement held out by the majority of publishers to write for glory, with perhaps a score of reprints thrown in, is about as unfair and unreasonable, not to use a harsher term, as anything can be — to the author, if his contribution is worth spreading before the public; to the public, who pay their money to the publisher, if it is not worthy. The excuse that long established custom sanctions such a procedure, is an unworthy one. Custom sanctions many an abuse, which is nonetheless an abuse. It is noteworthy that there are a few high-minded publishers who do not follow this course, but pay liberally for all contributions as is the custom with THE MEDICAL NEWS. In general literature, those journals earn the largest profits which pay their contributors most handsomely. Why would not the same rule apply equally in medical literature? It would lead to the decrease of many current publications — no doubt to a process of consolidation among some of the survivors, to a merciless sifting of wheat from chaff, and to more care and painstaking on the part of authors. All of which would conduce to the general improvement of medical literature.

From *Medical News*, December 17, 1887, p. 717-718.

Options For Controlling Costs: A Survey of the American Public and Selected Professionals in the Health Care Field

*Oh wad some power the giftie gie us
To see oursels as others see us!
It wad frae monie a blunder free us,
An' foolish notion.*

ROBERT BURNS

LOUIS Harris and Associates, Inc. have played the role of God and let us see ourselves. The Equitable Health-care Survey done by them for Equitable Life Assurance Society of the United States presents interesting contrasts between the views of doctors and those of a cross section of the public and of selected professionals in the health care field. Below are given the highlights of the survey.

1. There is a general consensus that fundamental changes are needed to make the U.S. health care system work better.

The American public, by a three-quarters majority, views the U.S. health care system as needing major changes. This view is shared by large majorities of employers, insurance executives, and unions, and by a marginal majority of hospital administrators. The one exception to this consensus lies with the medical profession: a clear majority of physicians who head medical societies believe that the health care system works pretty well and that only minor changes are needed to improve it.

2. The American public views both the cost of and access to health care services as areas in need of change.

Cost-related and access-related changes head the list of changes in the health care system considered most important by the American public and union leaders. The other professional groups acknowledge the need for cost-related changes, but they also emphasize public education regarding medical programs and costs. The primary change sought by physician leaders is less government interference and regulation.

The public's concern about access centers around care for the elderly. Based on their personal experiences, however, the American people, including the elderly, are largely satisfied with the quality of and access to health care services, and with health insurance benefits.

3. Barriers to medical care.

The 14% of the American public who did not obtain needed medical care in the twelve months preceding this survey include sizable numbers of the uninsured (32%) and the unemployed (28%). The primary barrier to obtaining needed medical care is the cost of this care.

4. There is widespread dissatisfaction with the cost of hospitalization.

While a slight majority of the American public are dissatisfied with the total cost of health care as well as out-of-pocket costs, their criticisms are focused mainly on the cost of hospitalization and the cost of laboratory work and X-rays done outside hospitals and clinics. Smaller majorities of the public also consider the cost of doctors' visits and prescription drugs to be unreasonable.

The view that hospital costs are unreasonable is shared by an overwhelming majority of union leaders, corporate benefits officers, and insurance executives, and by a significant majority of physician leaders. Even among hospital administrators, 40% view hospital costs as unreasonable.

5. There is very little consensus on the main cause of increased spending on health care.

The debate about the main underlying cause of the escalation of health care spending is still unresolved. While slightly more than 40% of the American people view this escalation as due to "the increasing cost of the same services," one-third of this group blame "the use of new and more expensive treatments and equipment." Physician leaders and hospital administrators view the latter reason as the primary cause of escalating expenditures.

"People using more services than they used to" is not acknowledged as a major cause of escalating expenditures by the American public. However, about 30% of physician leaders and hospital administrators recognize it as a primary cause of this escalation.

The views of corporate benefits officers and union leaders tend to parallel those of the public.

6. The health care system as it is today does little to encourage price competition.

Only 16% of the American public have selected a doctor because of lower fees. Comparison shopping for prescription drugs is viewed as easier than shopping for health insurance, doctors, or hospitals. Shopping for laboratory

From Equitable Life Assurance Society of the United States, 1285 Avenue of the Americas, New York, NY 10019.

tests and X-rays is viewed as difficult by a sizable majority of the American public.

7. The lack of price competition in the system is acknowledged as a reason for the rise in health care spending.

Large majorities of the American public and of all of the professional groups *except* the physician leaders agree that "the lack of competitive pricing among doctors, hospitals, or nursing homes" contributes to the rise in health care spending.

The opinions of physician leaders contrast sharply with those of all of the other groups, including hospital administrators. While only 37% of the physician leaders blame "lack of price competition" for the increase in health care spending, 68% of hospital administrators do so.

On the other hand, there is general consensus that as long as third-party payers assume all or most of the cost of health care, there is no incentive for patients or providers to cut spending or costs.

8. The American people and most professionals recognize that programs and practices that benefit them are also a source of inflation in health care spending.

Majorities in all groups mention the following as contributing to cost escalation: the increased availability of employer-paid health insurance, hospitalization for minor ailments, the growth of malpractice suits, people staying in hospitals longer than is necessary, the aging of the population, increased availability of government funded programs, and overuse of tests by doctors.

Physician leaders, in general, are least willing to recognize the actions of their own profession as contributing to the rise in health care spending, while hospital administrators have a more balanced view. While majorities of respondents in all groups recognize that "one of the problems in health care is that there is no real competition to keep prices down," only 27% of the physician leaders agree with this view.

9. The American public is ready to accept a broad range of cost-containment proposals.

The conventional wisdom that the American public will resist major changes in the health care system is called into question by the findings of this study.

The American public is remarkably willing to accept a broad range of cost-containment policies, including those that would increase out-of-pocket costs to the public and minimally curtail freedom of choice among health care options.

This willingness to accept proposed changes is based on the belief that the changes will be effective in slowing health care cost inflation. These findings suggest that the public would be willing to accept such changes because of a sense of realism and an understanding that the changes are necessary, rather than because they support them enthusiastically.

The proposals that the public considers most acceptable are: alternatives to the use of hospitals for minor surgery, tests, or the treatment of the chronically ill, increased cost-sharing in the payment of health insurance premiums

and increased deductibles, diagnosis-related cost caps on hospital and doctors' fees, requiring second opinions on non-emergency surgery, insurance rate incentives for preventive care, prepaid plans and preferred provider plans, and using low-cost alternatives to physicians and hospital care.

10. Professional groups have varying perspectives on the cost-containment proposals.

Union leaders, corporate benefits officers, and insurance executives generally share the views of the American public, and they are willing to accept almost all of the proposed changes in the health care system.

Hospital administrators are generally willing to accept changes in the health care system in the interest of cost containment, even if the changes mean a reduction in hospital use or a restriction on the fees charged by hospitals.

Physician leaders are the least willing of all groups surveyed to accept — or even to recognize as effective — changes that are likely to adversely affect the financial incentives for their profession.

11. Most corporate executives whose companies have implemented new cost-containment programs believe that the programs are effective.

Corporate executives whose organizations have had experience with various cost-containment measures are more likely to judge them as effective than are those who have had no experience with these measures. This is particularly true for programs that require increased cost-sharing by employees and for those that provide better coverage for lower cost health care options, such as home care for the chronically ill and the use of nurse practitioners, midwives, and physicians' assistants.

12. There is widespread opposition to a proposed tax on employer-paid premiums.

One policy that is rejected by the majority of respondents in most groups as ineffective and unacceptable as a cost-containment measure is the often-discussed individual tax on a portion of the employer-paid health insurance premiums. The physician leaders are the only group in which a clear majority find this proposal to be both effective and acceptable.

13. Shifting costs from Medicare patients to other patients is viewed with disfavor.

The majority of the American public and majorities of all of the professional groups disapprove of the practice of shifting costs from Medicare patients to other patients. This disapproval is voiced as strongly by those who do receive Medicare benefits as those who do not.

14. There is general support for programs that provide health insurance for the unemployed, but it diminishes sharply when viewed as resulting in greater costs for other people.

The American people (including the unemployed) and corporate benefits officers reveal a marginal reluctance to support health care benefits for the unemployed if such

benefits result in higher direct or indirect costs to other people. However, sizable minorities (of more than 40%) are in favor of these benefits despite their costs.

Physician leaders, insurance executives, and hospital administrators, on the other hand, favor providing these benefits.

15. Overall, the American public reveals awareness of and concern about health care issues.

The majority of the American public are remarkably aware of and concerned about problems related to health care coverage and health care services. This is reflected in the relatively insignificant numbers of respondents who give "not sure" or "no opinion" responses to the questions asked in this survey.

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If you still believe in me, save me.

For nearly a hundred years, the Statue of Liberty has been America's most powerful symbol of freedom and hope. Today the corrosive action of almost a century of weather and salt air has eaten away at the iron framework; etched holes in the copper exterior.

On Ellis Island, where the ancestors of nearly half of all Americans first stepped onto American soil, the Immigration Center is now a hollow ruin.

Inspiring plans have been developed to restore the Statue and to create on Ellis Island a permanent museum celebrating the ethnic diversity of this country of immigrants. But unless restoration is begun now, these two landmarks in our nation's heritage could be closed at the very time America is celebrating their hundredth anniversaries. The 230 million dollars needed to carry out the work is needed now.

All of the money must come from private donations; the federal government is not raising the funds. This is consistent with the Statue's origins. The French people paid for its creation themselves. And America's businesses spearheaded the public contributions that were needed for its construction and for the pedestal.

The torch of liberty is everyone's to cherish. Could we hold up our heads as Americans if we allowed the time to come when she can no longer hold up hers?

Opportunities for Your Company.



You are invited to learn more about the advantages of corporate sponsorship during the nationwide promotions surrounding the restoration project. Write on your letterhead to: The Statue of Liberty-Ellis Island Foundation, Inc., 101 Park Ave, N.Y., N.Y. 10178.



Save these monuments. Send your personal tax deductible donation to: P.O. Box 1986, New York, NY 10018 **The Statue of Liberty-Ellis Island Foundation, Inc.**

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**BP-SPEC
1983**

Computer Diagnoses

Devereux H. Lippitt, M.D.

WHAT about these interpretive computer programs that juggle laboratory data and come up with a list of diagnoses or interpretations? They have been around for years but lately there is a push by laboratory suppliers to sell the hardware and programs together in a single package. Computers have had their greatest use in adding qualifying comments on a single unusual test when the result is out of range. In fact, in a community hospital most of the rarely done tests will be sent to central commercial laboratories, and cautions concerning false positives, interfering drugs, and so forth are added to the reports. The computer has merely located the comment and printed it, much like an aide could do with a rubber stamp.

Greater complexity is involved when a combination of tests is used to arrive at an interpretive comment or diagnosis. The decision tree or algorithm is the ultimate in formal logic but few problems can be solved in this way since so many consecutive yes/no answers are required. Instead, by rapid but obscure mathematical manipulations such as multivariate data analysis a computer may reach a decision based on many items of quantitative data. The weather is predicted with greater than human accuracy by this method. In medicine, risk factors can be calculated and the percentage risk for a given diagnosis given. This may help

an inexperienced physician or a paramedic estimate the need for surgery or a CAT scan. If the risk were too low, perhaps the intermediary would have a rule not to pay.

Some of the older sorting methods for diagnosis from SMA 12 reports were based on punch cards and could yield a variety of diagnoses sometimes more humorous than valuable. Such methods never enjoyed sustained popularity. When a pattern of numbers or multivariate analysis is used for interpretation rather than individually significant data, management based on this might have a medieval aura. This recalls Montaigne's aphorism: "It is more of a job to interpret the interpretations than the things, and there are more books about books than any other subject." The instantaneous elimination or tolerance of absurd possibilities might itself require much judgment and knowledge.

The method of the mind in diagnosis differs entirely from the computer. We leap to answers often based on equivocal data simply by intuition. Sometimes illogical ideas or dimly remembered similarities can lead to a solution. How to program computers to use such heuristic methods of thinking which are quite efficient and effective continues to occupy and baffle mathematicians.

When we recall that 85-90% of diagnoses on clinically ill patients are made from the history and physical, the possibilities left for the computer to shine are largely interpretive rather than diagnostic. It's going to be interesting to see if the laboratory supply houses can sell these programs these next few years.

From Craven County Hospital Corporation, P.O. Box 2157, New Bern 28560.

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IN STATE

April 25

"Current Concepts in Otolaryngology for the Primary Physician"

Place: UNC
Fee: \$50
Credit: 6½ Hours
Info: B. Neilson, UNC School of Medicine, 231 MacNider Bldg 202H, Chapel Hill 27514. 919/962-2118

April 28

Alzheimer's Disease Update

Place: UNC
Fee: \$15
Credit: 5 hours
Info: B. Neilson, UNC School of Medicine, 231 MacNider Bldg 202H, Chapel Hill 27514. 919/962-2118

May 10-11

Infectious Disease Update 1984

Place: Greensboro
Fee: \$75
Credit: 11 hours Category I AMA
Info: Fred Levick, Greensboro AHEC, 1200 North Elm Street, Greensboro 27401. 919/379-4025

May 10-12

North Carolina Chapter of the American College of Surgeons

Place: Boone
Info: Richard W. Furman, M.D., 702 State Farm Road, Boone 28607. 704/264-2340

May 16

Progress on Type 2 Diabetes

Place: Raleigh
Fee: None
Credit: 3 hours
Info: B. Neilson, UNC School of Medicine, 231 MacNider Bldg 202H, Chapel Hill 27514. 919/962-2118

May 17-18

Social Behavior in Autism

Place: Chapel Hill
Fee: \$25 in-state; \$100 out-of-state
Credit: 12 hours
Info: B. Neilson, UNC School of Medicine, 231 MacNider Bldg 202H, Chapel Hill 27514. 919/962-2118

May 17-19

Floyd W. Denny Alumni Lecture Series

Place: Chapel Hill
Info: Gerald W. Fernald, M.D., Pediatrics, 509 Burnett-Womack Bldg. 229H, UNC School of Medicine, Chapel Hill 27514. 919/966-2085

May 18-20

Pathokinesiology of Cerebral Palsy

Place: Chapel Hill
Info: Darlene S. Slaton, Physical Therapy, C 221H, UNC School of Medicine, Chapel Hill 27514. 919/966-4708

May 25-26

13th Annual Seminar: Gut and Lung Problems in Pediatrics

Place: Durham
Credit: 12 hours

Fee: \$60
Info: Alexander Spock, M.D., Box 2994 Duke University Medical Center, Durham 27710. 919/681-3364

May 25

Pediatrics Day

Place: Greenville
Credit: 7 hours
Fee: \$55
Info: Mary C. Valand, Box 7224 ECU School of Medicine, Greenville 27834. 919/758-5200

May 31-June 2

The Sea Level Invitational Conference on Geriatric Medicine

Place: Sea Level
Info: M. Valand, ECU School of Medicine, PO Box 7224, Greenville 27834. 919/758-5200, ext 208

May 31-June 2

Approaches to Ethical Decision Making

Place: Durham
Info: Nettie Wilburn, UNC-CH School of Nursing, Carrington Hall 214H, Chapel Hill 27514. 919/966-3638

June 1-2

Neurology for the Primary Physician

Place: Chapel Hill
Fee: \$100
Credit: 11 hours
Info: B. Neilson, UNC School of Medicine, 231 MacNider Bldg 202H, Chapel Hill 27514. 919/962-2118.

June 5

Duke Tuesday

Place: Durham
Credit: 5 hours
Info: L. Mace, Urology, Duke U Med Center, Box 3707, Durham 27710. 919/684-2033

June 6-7

Fellows Symposium

Place: Chapel Hill
Info: John J. Frey, M.D., 231 MacNider Bldg 202H, Chapel Hill 27514.

June 17-22

Health Promotion — Wellness Institute

Place: Raleigh
Fee: \$250
Credit: 30 hours
Info: NC Health Promotion, Wake AHEC, 3000 New Bern Ave, Raleigh 27610. 919/755-8018

June 22-23

North Carolina Affiliate, American Heart Association, 35th Annual Meeting and Scientific Sessions

Place: Durham
Info: N.C. Heart Association, Chapel Hill 27514

July 9-14

26th Annual Postgraduate Course/Morehead Symposium

Place: Atlantic Beach
Credit: 25 hours
Info: C. Easterling, Duke U Medical Center, Box 3306, Durham 27710. 919/684-6485

OUT OF STATE

April 9-11

"Gold Coast Seminar: OB/GYN"

Place: West Palm Beach, FL
Credit: AMA, AAFP
Info: Continuing Medical Education, Box 3306, Duke University Medical Center, Durham 27710. 919/684-6485

May 7-9

Gold Coast Seminar: Medicine

Place: West Palm Beach, FL
Credit: AMA, AAFP
Info: Continuing Medical Education, Box 3306 Duke University Medical Center, Durham 27710. 919/684-6485

May 10-12

Current Concepts of Clinical Infectious Diseases

Place: Hot Springs, VA
Fee: \$220, \$165, \$295
Credit: 13 3/4
Info: Gerald L. Mandell, M.D., Univ of Virginia, Charlottesville

May 18-19

Practical Dermatology for the Non-Dermatologist
Place: Williamsburg, VA
Fee: \$90
Credit: 7 hours
Info: B. Neilson, UNC School of Medicine, 231 MacNider Bldg 202H, Chapel Hill 27514. 919/962-2118

May 24-27

8th Annual Radiology Symposium
Place: Hilton Head, SC
Fee: \$350
Credit: 19 hours
Info: B. Neilson, UNC School of Medicine, 231 MacNider Bldg 202H, Chapel Hill 27514. 919/962-2118

May 30-June 2

AACA 1984 Spring Seminar in Anesthesiology
Place: Hilton Head, SC
Info: Amer Academy of Clinical Anesthesiologists, P.O. Box 11691, Knoxville, TN 37939-1681. 615/588-6279

May 31-June 2

The Sea Level Invitational Conference on Geriatric Medicine
Place: Sea Level, GA
Info: Mary C. Valand, CME, ECU School of Medicine, Greenville 27834. 919/758-5200

June 4-8

Cornell University Diagnostic Radiology Update Emphasizing Advances in Imaging and Interventional Procedures
Place: Bermuda
Credit: 100 hours
Fee: \$400, \$300
Info: Ann Wold, Gallagher/Wold, Inc., 420 Lexington Ave., New York 10170. 212/986-1277.

June 27-30

Dermatology for Non-Dermatologists
Place: Myrtle Beach, SC
Credit: 15.5 hours Category 1 AMA
Fee: \$350
Info: Dermatology, Box 2987 Duke University Medical Center, Durham 27710. 919/684-6728

July 2-7

Midsummer Family Practice Digest
Place: Myrtle Beach, SC
Credit: 30 hours
Info: NCAFP. 919/781-6476

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DURHAM-ORANGE

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Douglas Carter Anthony (Student), Box 2710, Duke Medical Center, Durham, NC 27710
Andrew Nicholas Antoszyk (Resident), 1801 Williamsburg Road 35B, Durham, NC 27707
Dorothy Duncan Baker (Student), Box 2708, Duke Medical Center, Durham, NC 27710
Deirdre Vance Batch (OBG), 226 Indian Trail Road, Chapel Hill, NC 27514
Martha Jane Bennett (IM), 1901 Hillandale Road, Durham, NC 27705
Charles Arthur Bolick (Student), 9-B University Lake Apts., Carrboro, NC 27510
Eric Barnett Carlson (Resident), 24 Astor Court, Durham, NC 27705
David Ruddle Carr (Student), Box 2709, Duke Medical Center, Durham, NC 27710
David Allen Coggin (Student), Royal Park Apts. Apt. 12E, Carrboro, NC 27510

Joseph Michael Cools (P), Box 2995, Duke Med. Center, Durham, NC 27710

Sarah Byrd Cornwell (Student), Box 2829, Duke Medical Center, Durham, NC 27710

Angela Faye Crisp (Student), 68 Fernwood Lane, Chapel Hill, NC 27514

Sharon Ruth Cumbee (Student), Box 2716, Duke Medical Center, Durham, NC 27710

Laurence E. Dahners (ORS), 712 Clearwater Lake Road, Chapel Hill, NC 27154

Thomas Noel Darling (Student), Duke Manor Apt. 46-M, 311 S. Lasalle St., Durham, NC 27705

David Howard Darrow (Student), 2752 Middleton Ave. Apt. 28K, Durham, NC 27705

Stephen Edgar Deal (Student), 114 Purefoy Road, Chapel Hill, NC 27514

Katherine Anne Enright (Student), Box 2737, Duke Medical Center, Durham, NC 27710

David Worth Frazier (Student), 1315 Morreene Rd. Apt. 11-M, Durham, NC 27705

Donald Paul Frush (Student), 4411 Ryan St., Durham, NC 27704

William Stephen Furr (Student), Box 2761, Duke Medical Center, Durham, NC 27710

Matthew Alan Galumbeck (Student), Box 2883, Duke Medical Center, Durham, NC 27710

Herbert Gaston Garrison, III (Student), 623 Hibbard Drive, Chapel Hill, NC 27514

Judie Lynne Garrison (Student), 623 Hibbard Drive, Chapel Hill, NC 27514

Jack Jay Gelman (Student), 1315 Morreene Rd. Apt. 5-F, Chapel Tower Apts., Durham, NC 27705

John Russell Gilmore (Resident), Otolaryngology Clinic, Duke Univ. Medical Center, Durham, NC 27710

Alexander E. Reginald Gonzalez (Student), 2706 Hillsborough Road, Durham, NC 27705

Marc Harris Gorelick (Student), Box 2729, Duke University Medical Center, Durham, NC 27710

Steven J. Gulevich (Student), Box 2762, Duke Medical Center, Durham, NC 27710

Langdon All Hartsock (Student), 311 S. Lasalle St., Apt. 29-B, Durham, NC 27705

Linn Haynes Hatley (OBG), Durham Women's Clinic, 1821 Green Street, Durham, NC 27705

Wendy Hawke (Resident), 9 St. James Court, Durham, NC 27713

Miriam Virginia Hughes (Student), 16-B Estes Park Apts., Carrboro, NC 27510

Cheryl Ann Hillery (Student), Box 2705, Duke Medical Center, Durham, NC 27710

Catherine Carroll Hobbs (Student), 1611 Budwood Drive, Raleigh, NC 27609

John Harry Holtkamp (Resident), 158 Windstone, Pittsboro, NC 27312

Paul Harutaka Yoshino (Student), Box 2820, Duke Medical Center, Durham, NC 27710

Dudley Allen Hudspeth (Student), 300 Barnes St. Apt. 10A, Carrboro, NC 27510

Robert Lee Jobe (Student), 201 Howell Street, Apt. 2B, Chapel Hill, NC 27514

Alfreda Jones (Student), UNC, 353 Craige Dormitory, Chapel Hill, NC 27514

Daniel James Kenan (Student), Box 2738, Duke Medical Center, Durham, NC 27710

Rebecca Smith Kennedy (Student), Route #10, Box 116, Chapel Hill, NC 27514

Allan Douglas Kirk (Student), Box 2739, Duke Medical Center, Durham, NC 27710

Dennis Demosthenes Kokenes (Student), R-12 Old Well Apts., Carrboro, NC 27510

Julie Ann Kreager (Student), Box 2740, Duke Medical Center, Durham, NC 27710

Catherine Mary Kuhn (Student), 405 Ransom St. Apt. 101, Chapel Hill, NC 27514

Thomas Earl Lawrence (Student), K-8 Tar Heel Manor Apts., Carrboro, NC 27510

Stephen Lesher Leighton (FP), P.O. Box 12833, 22 Park Plaza, Research Triangle Pk, NC 27709

Michael John Lemanski (Resident), 3600 Tremont Dr. Apt. A-8, Durham, NC 27705

Cyril Yiu-Chun Leung (Student), Box 2745, Duke Medical Center, Durham, NC 27710

Manuel Eugenio Lores-Suarez (Resident), 128 Ridge Trail, Chapel Hill, NC 27514

Wylie Donald Lowery (Student), Brighton Square, Apt. #40, Carrboro, NC 27510

Gustav Magrinat (Student), 2005 S. Lakeshore Dr., Chapel Hill, NC 27514

Paul Joseph Mainella (Student), 57 Laurel Ridge Apts., Chapel Hill, NC 27514

David Tupper Manly (Student), 300-C Mason Farm Road, Chapel Hill, NC 27514

James Peter Manor (FP), 602-S Jones Ferry Road, Carrboro, NC 27510

Stuart Gary Marcus (Student), Box 2747, Duke Medical Center, Durham, NC 27710

Mark Edward Mayer (Resident), 124 Lady Bug Lane, Chapel Hill, NC 27514

Jayne Patrice Maynor (Student), UNC, 353 Craige Hall, Chapel Hill, NC 27514

Holman Page McAdams (Student), 2116 Front St. Apt. B-8, Durham, NC 27705

Julia Winn McCutcheon (Student), 4300 Erwin Road, Durham, NC 27705

Marsden Hamilton McGuire (Student), 1320-10 Ephesus Church Rd., Chapel Hill, NC 27514

Joyce Marie McKenney (Resident), 1207-B Carroll, Durham, NC 27707

Robert Eric McNeill (Student), Box 2886, Duke Medical Center, Durham, NC 27710

Lynne Bennett Meador (Student), Box 2749, Duke Medical Center, Durham, NC 27710

Pamela Dawn Mohr (Student), Box 2753, Duke Medical Center, Durham, NC 27710

Robert Bruce Montgomery, Jr. (Student), Box 2754, Duke Medical Center, Durham, NC 27710

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Helen Mary O'Donnell (Resident), 714 Shepherd Street, Apt. A, Durham, NC 27703

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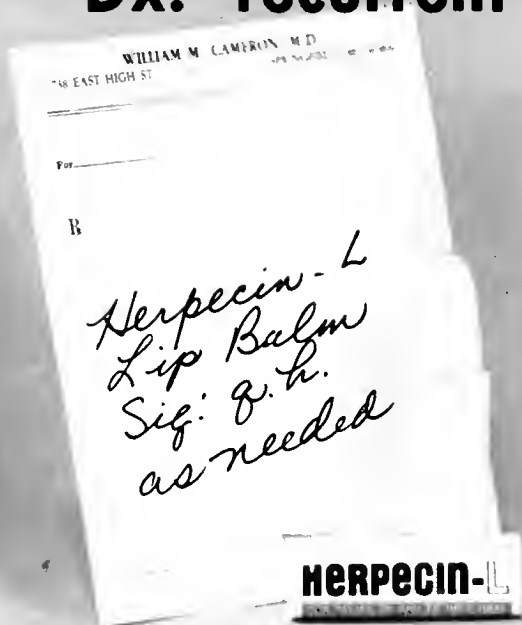
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WILLIAM LESTER ADCOCK, JR., M.D.

Dr. Adcock, who died on August 26, 1983 arrived in Raleigh to practice neurosurgery nineteen years ago. He came well-educated, holding gold keys as evidence of his successes in scholarship at the college and medical school levels, and well-trained in his specialty. Dr. Adcock served as President of the Wake County Medical Center staff in 1980.

Dr. Adcock, the oldest of five children, grew up in Rockingham, N.C., admiring a highly respected local physician, whose career served as a model. For college admission Dr. Adcock applied only to the then Wake Forest College, the only university he wished to attend. Recognizing his intellect, they took him. Subsequently he attended the Bowman Gray School of Medicine. Dr. Adcock served as a Captain, U.S. Army, 1957-1959, assigned to the 2nd General Hospital, Landstuhl, Germany, providing neurosurgical support for the U.S. Army ground forces in Europe

and the Sixth Fleet in the Mediterranean.

Dr. Adcock had a wide variety of interests and hobbies: collecting classical music records, coins, stamps, and army vehicles. He was a great connoisseur of wine, food and flowers. Roses were his special favorite. A much admired rose garden is planted beside his office and he often wore a rose in his lapel.

While eminently memorable as a practitioner, it was as a person that he was most unforgettable. He was a classic example of a man whose gruff manner served as a facade to cover a gentle nature and a generous heart. On at least one occasion he purchased a hospital bed for home use by one of his pediatric patients. His devotion to his family was intense. He spoke often of the joy of his marriage to Naomi and his pleasure in his relationships with his three children, Catherine Ellen, a dental hygienist; Dorothy Elizabeth, a second year medical student at her Dad's alma mater; and Jeffrey David, now in his sophomore year in Computer Science at Chapel Hill.

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Letters to the Editor

Mediation Committee Reports on Complaints

To the Editor:

The North Carolina Medical Society Mediation Committee continues to have numerous complaints from patients regarding records of physicians. The following is a statement from the AMA Judicial Council Current Opinion regarding availability of information.

"The AMA believes the interest of the patient is paramount in the practice of medicine, and everything that can reasonably and lawfully be done to serve that interest must be done by all physicians who have served or are serving the patient. A physician who formerly treated a patient should not refuse for any reason to make his records of that patient promptly available on request from another physician presently treating the patient. Proper authorization for the use of records must be granted by the patient. Medical records should not be withheld because of an unpaid bill for medical services.

"According to the AMA, notes made in treating a patient are primarily for the physician's own use and constitute his personal property. However, on request of the patient a physician should provide a copy or a summary of the record to the patient or to another physician, an attorney or other person designated by the patient. Several states have enacted statutes that authorize patient access to medical records. These statutes vary in scope and mechanism for permitting patients to review or copy medical records. Access to mental health records, particularly, may be limited by statute or regulation. A physician should become familiar with the applicable laws, rules or regulations on patient access to medical records. The record is a confidential document involving the physician-patient relationship and should not be communicated to a third party without the patient's prior written consent, unless required by law or to protect the welfare of the individual or the community. Medical reports should not be withheld because of an unpaid bill for medical services. Simplified, routine insurance reimbursement forms should be prepared without charge, but a charge for more complex, complicated reports may be made in conformity with local custom."

The Mediation Committee also receives complaints from members of the family regarding information concerning illness of a loved one. We feel that more communication between the physician and family members during serious illness and especially in the death of a patient would alleviate many of these complaints. More detailed information to members of the family especially in critical illnesses or death of the patient would show sincere consideration and compassion by the physician and would certainly be most appreciated by the family.

D. E. Ward, Jr., M.D., Chairman
Mediation Committee, NCMS
2604 North Elm Street
Lumberton 28358

Davison Stories Keep Coming

To the Editor:

Dr. Davison was made a Master of the American College of Physicians and was the only pediatrician to receive this honor. The meeting was in Chicago and we went out together.

On the trip we were talking about Dave's trip to England at the end of World War II in Europe. Dave was one of a group of VIPs waiting in Washington, D.C. to get a government flight to London. He was on his way to visit the Duke Unit, the 65th General Hospital stationed at Redgrave Park in Suffolk, in support of the 8th Air Force.

A few hours before the flight to London, VE Day occurred and all the military brass on the flight cancelled out. Dave found himself taking off on a huge Army transport to London as the only passenger. About four hours into the flight over the Atlantic he decided to go to the flight area and speak to the crew for a chat. Much to his amazement, there was no one in the pilots' area. The plane was on automatic pilot and the crew was below for coffee.

When I went to pick him up in a jeep at ETO headquarters in London to take him out to the 65th General Hospital, he was still recovering from his unique trip.

Joseph B. Stevens, M.D.
1017 Professional Village
Greensboro

Some Problems Have Solutions

To the Editor:

For many years, organized medicine has been on the defensive, fighting one brush fire or another.

May I suggest that now is an excellent time for us to become positive and provide some leadership for the nation.

I. PROBLEM

Medicine is now being criticized and partially rightly so for the cost of medical care. There are many facets to this problem.

1. Medicine in 1984 is expensive because America is receiving some of the best medical care in the world — that's good.
2. Medicine in 1984 is expensive because we are practicing defensive medicine.
 - a. Malpractice premiums are up because there are more and larger suits. These premiums ultimately come from the patient.
 - b. We do more lab studies and hospital procedures than necessary as a defense against malpractice problems. This expense ultimately comes from the patient.

Throw your brain out of gear for a few moments and let's see how we can attack this part of the problem. I do not

propose to have all the answers, but let's toy with a few ideas.

II. SOLUTION

Let's let organized medicine, the North Carolina Medical Society, the North Carolina Hospital Association, medical insurance companies, etc., pool our brain power and take the lead in a solution to help medicine and to help the patient. Let's cut some of these costs.

Let's try the following for a starter:

1. Let's jointly ask the Legislature to make arbitration a fact in North Carolina.
2. Let's get the insurance companies to offer medical insurance to large companies and individuals so that the co-insurance required from the patient

is less if the recipient signs a waiver stating that he is willing to abide by arbitration if a dispute arises.

3. Let the M.D. have a guaranteed reduction in malpractice premiums if he signs a waiver stating that he is willing to abide by arbitration if a dispute arises.

If the patient, the insurance companies, we the people, and the M.D.'s all win, then it is a good game.

Bruce B. Blackmon, M.D.
Fifth District Councillor
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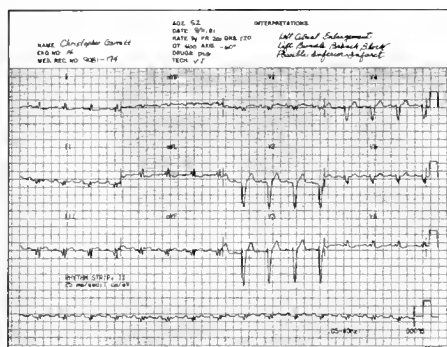
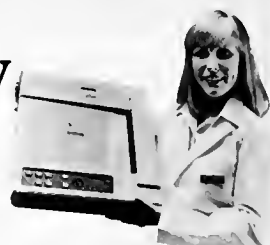
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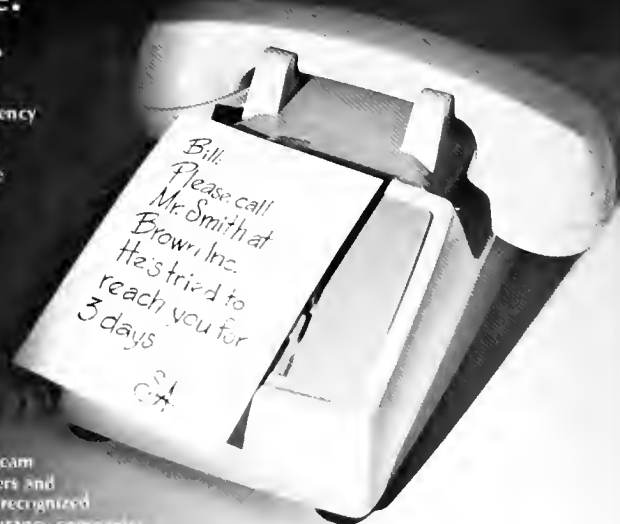
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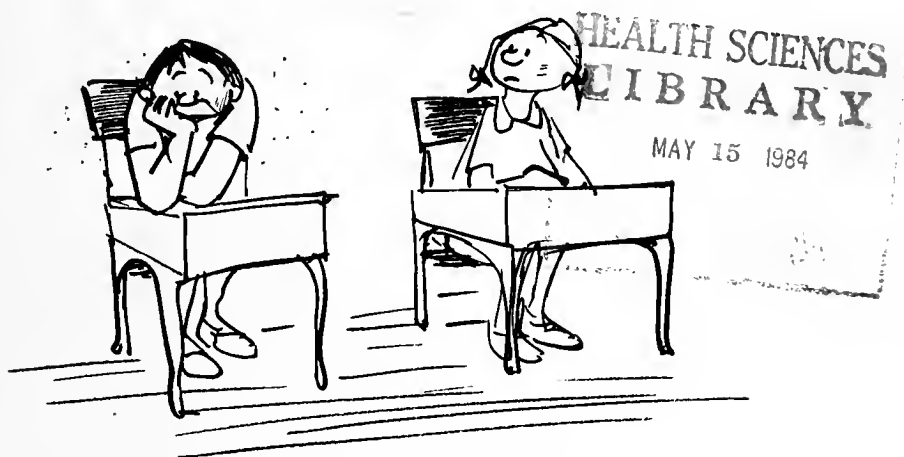
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May 1984, Volume 45, No. 5

The Patient Has a Sore Throat

By school age, children have five to six upper respiratory infections per year. Parents worry about strep throats and rheumatic fever. What should the patient and doctor do?

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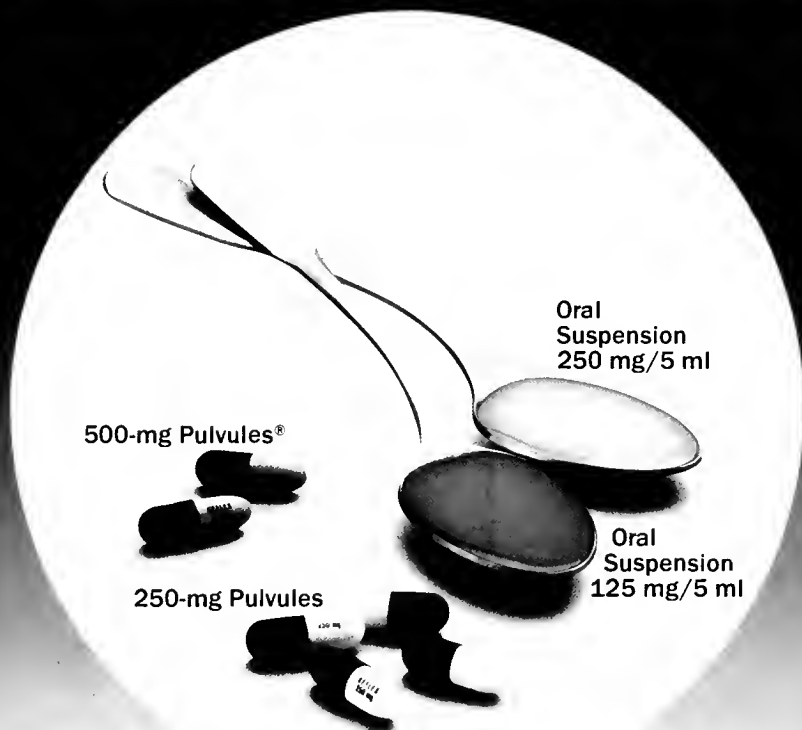
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To Comfort Always: Strategies for Pain Management in Terminal Cancer

Linda M. Frazier, M.D. and Errol J. Kohl, R.N., B.S.N.

"To cure sometimes, To relieve often, To comfort always."

Fifteenth century folk saying on the duties of a physician.

OPIUM has been used since Babylonian times and injectable morphine has been available since before the Civil War. Despite this prolonged opportunity to learn how to use narcotic analgesics, physicians often use them poorly in managing pain.¹ This is in part because pain has many faces: strategies that work well for the acute self-limited pain of renal colic or trauma are neither appropriate nor

effective for chronic low back pain or porphyria. The pain of cancer in its early stages can be managed like pain from other causes, but when the cancer becomes advanced pain becomes more complex and additional strategies are needed. The following case illustrates strategies for managing severe pain in terminal cancer.

A patient with advanced cancer presented with abdominal pain.

Case: A thirty-one-year-old man developed progressive abdominal pain and weight loss. At a local hospital he was found to have gastric adenocarcinoma with metastases to the posterior abdominal wall and para-aortic lymph nodes. He received radiotherapy and 5-fluorouracil but deteriorated over the next seven months and was referred for evaluation of severe abdominal pain, wasting and ascites. His only medication was Demerol, 100 mg intramuscularly (IM), every four hours.

A team of two physicians began caring for him. Physical examination revealed an alert, oriented, cachectic man in moderate distress from abdominal pain. Blood pressure was 130/110 mm Hg and respirations were 22 per minute. There was dullness at both lung bases. The abdomen was tender and tensely distended with shifting dullness and prominent venous collaterals; pitting edema extended to the knees; axillary and inguinal lymph nodes were enlarged. Hemoglobin was 8.2 mg/dl (normal 12-17), creatinine was 2.1 mg/dl (normal 0.6-1.6), and albumin was 3.1 g/dl (normal 3.9-5.4).

The physicians made plans to evaluate his tumor.

In their initial assessment, his physicians commented on the rarity of gastric cancer in a thirty-one-year-old and they speculated at length about the cause of his ascites. They felt the patient was "preterminal" and wanted to make him comfortable, but they asked four consultants to recommend further cancer treatment. They considered performing an abdominal paracentesis, lymph node biopsy, renal sonogram and a creatinine clearance. They thought about beginning iron therapy, about improving his nutrition and about helping him spend time with his family. Instead, they ordered serum transaminases, a hepatitis B surface antigen, VDRL, and an abdominal x-ray. They prescribed milk of magnesia, Colace and Tylox, two capsules by mouth every six hours as needed for pain.

From the Department of Medicine, Duke University Medical Center, Durham 27710.

The physicians did not make a pain assessment.

They did not make a pain management plan.

Comment: The doctors caring for this unfortunate patient correctly concluded that he did not have long to live because the prognosis of unresectable gastric cancer is poor and because physical exam showed that the tumor was widespread. They also decided appropriately to make him comfortable. But they found it difficult to achieve this goal. They would have been able to make this patient more comfortable by using several basic pain control strategies, which we discuss below.

It is remarkable that the primary physician duly recorded "abdominal pain" as the patient's chief complaint, but then failed to mention it in his three-page case assessment. Although he wanted to make the patient comfortable, he did not plan explicitly to do so. His associate made a twelve-item problem list, but did not include abdominal pain as one of the problems. Both physicians thought about the cancer and tests that could measure its spread but they overlooked the patient's significant pain. They made explicit plans to evaluate and treat every aspect of his disease except pain.

In contrast, a consulting internist considered pain control the most important objective and the nurse's major plan was to administer pain medications promptly at the patient's request. Nevertheless, the first analgesic order was haphazard, reflecting the fact that the doctors had made no pain assessment or pain management plan at the outset: For this patient with severe pain caused by advanced cancer, they prescribed Tylox, two capsules by mouth every six hours as needed. This is much less analgesia than the Demerol given at the other hospital. Furthermore, the Tylox was ordered only "as needed for pain," and not on a regular basis.

Pain Management Strategies

1. Make a pain assessment.

Pain control may be the only thing the physician can do for a terminal cancer patient, but this goal must be identified before it can be achieved. A successful pain management strategy depends on an accurate baseline pain assessment and frequent follow-up assessments. The pain assessment may be difficult because patients express themselves in different ways. Many patients feel that their pain is typical of their disease and that doctors and nurses must already know how much pain they are experiencing; they may feel that if pain medication were necessary the doctor or nurse would surely give it. Other patients stoically wait until their pain is unbearable before they mention it. This can lead to poor pain management when the doctor or nurse believes that patients will always request pain medication if they are in pain. Doctors and nurses should ask themselves whether any other attitudes are influencing their pain assessment. Do we assume that patients with the same disease should have the same amount of pain? Do we doubt patients who express their pain in a culturally unacceptable manner? Do we doubt patients who complain of severe pain but lack "signs" of pain such as tachycardia, diaphoresis, grimacing or protective movements? These sympathetic physiologic responses that are so often present in acute pain may be absent or less pronounced in chronic pain because the patient is unable to maintain a constant state of "fight or flight."

We may also assume incorrectly that a cancer patient's pain is always caused by the cancer. It is important to determine whether the pain arises from the primary tumor and metastases or from secondary complications such as ulceration, infection, obstruction of a hollow viscus, pathologic fracture or compression of nerves by fibrosis or collapse of structural supports. These secondary complications should be treated with local hygienic measures, antibiotics, splints or surgery. Patients with advanced cancer are less able to tolerate pain if they suffer from foul-smelling discharges, dyspnea, dysphagia, nausea and vomiting, intractable cough or hiccups, or profound fear of disfigurement, invalidism, isolation or death. Pain control is easier to achieve when these symptoms are treated and psychological support is given.

It is important to quantitate the pain caused by the tumor and metastases. Get an idea of how frequently pain interferes with daily activities. Ask whether the pain is present throughout the day and whether it keeps the patient from sleeping. How many hours does the patient sleep? What analgesics have been tried? How long does relief last after each dose? It is often helpful to ask patients to rate their pain on a scale from zero to ten, with ten representing the worst pain imaginable. Serial pain ratings can then be used to measure the effect of therapy. Think of pain as a medical problem like any other problem. Quantitate its severity as well as possible and note what treatments have already been

ried; use this information to plan the next phase of treatment. Because pain is so different for each patient, the initial assessment can not provide all the information necessary for formulating a successful pain management plan. It is crucial to reassess pain frequently and modify the pain management strategy as needed.

2. Make a pain management plan.

The goal of therapy is to provide complete pain relief without impairing cognition or other physiologic functions. Sometimes it is not possible to obtain one hundred percent pain relief because as the narcotic brings pain down to a tolerable level, the patient may decide that further analgesia is not worth an increase in narcotic side effects such as constipation or drowsiness. The goal in these patients is to keep pain from interfering with daily activities; this is an achievable goal.

Psychological support is important. Palliative radiotherapy, chemotherapy or surgery should be used if warranted, and secondary complications of the tumor should be treated. Thereafter, narcotics are the mainstay of therapy. Don't waste time on analgesic therapy that has failed in the past. In order to do this, one must be able to compare the potency of different analgesic regimens as described next.

3. Calculate equivalent doses of narcotic analgesics.

When caring for patients with terminal cancer, it is likely that the physician will have to change from one analgesic to another at some point. The most common change is from an analgesic taken by mouth to a parenteral narcotic. Before any narcotic analgesic is marketed, careful potency studies determine how much of the new drug will provide pain relief equivalent to a standard drug such as morphine. Tables showing equivalent narcotic doses are available in

the pharmacy literature; unfortunately, they have not yet been included in major medical textbooks. With a narcotic equivalence table, one can calculate the relative potency of different analgesic regimens and derive a drug dose to provide as much or more analgesia as regimens used previously.

As an example, let us compare the Tylox ordered when our patient was admitted, to the Demerol he had been receiving at the referring hospital. We first convert the dose of each drug to Analgesic Units (we define one Analgesic Unit as the amount of analgesia provided by one mg of Demerol administered intramuscularly). Demerol, 100 mg IM every four hours, provides 600 Analgesic Units per day (table 1).² Each Tylox capsule contains 4.5 mg of oxycodone hydrochloride, so two capsules by mouth every six hours provide 90 Analgesic Units per day. This Tylox regimen is less than one-sixth as potent as the parenteral Demerol had been and understandably did not relieve our patient's pain.

4. Order analgesics around the clock for constant severe pain.

The pain of advanced cancer is usually constant. When analgesics are administered "p.r.n.," the patient is placed on a roller coaster and forced to reexperience pain before he can receive the next dose of pain medication. The patient anticipates severe pain as analgesia wears off; he or she becomes anxious and pain is more difficult to relieve. It is better to get pain under control and then keep it from recurring by giving analgesics at regular intervals around the clock. Patients often achieve better pain control with a lower narcotic dosage when doses are given around the clock rather than "p.r.n."

Table 1
Narcotic Conversion Table: The relative potency of narcotic analgesics compared to parenteral Demerol

Drug Generic name	Trade name	Analgesic Units* per mg	
		Intramuscular	Oral
Meperidine	Demerol	1.0	0.25
Morphine	—	7.5	1.25
Methadone	Dolophine	7.5	3.75
Codeine	—	0.63	0.38
Oxycodone	Tylox, Percodan	5.0	2.5
Hydromorphone	Dilaudid	50	10

*One Analgesic Unit is the amount of analgesia provided by one mg of Demerol administered intramuscularly. To use this table to calculate doses of equal potency when switching from one narcotic to another, convert each dose (mg) to Analgesic Units. For example, a Tylox capsule contains 4.5 mg oxycodone; two capsules by mouth contain 22.5 Analgesic Units (9×2.5) and are equivalent to Demerol, 22.5 mg IM. Morphine, 10 mg IM contains 75 Analgesic Units (10×7.5). (Table derived from Lewis BJ, in *Cancer, Principles and Practice of Oncology* (DeVita VT ed), Philadelphia, JB Lippincott Co., 1982, pp. 1658-1665.)

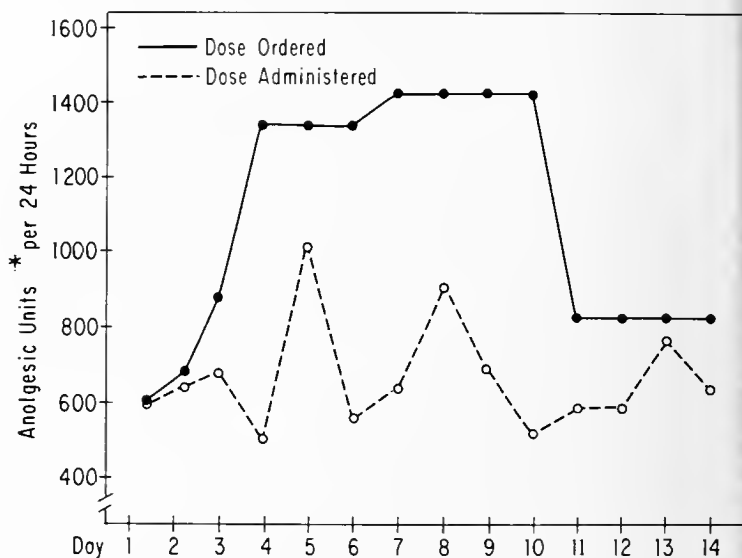
Over seven days the analgesic dose was gradually increased.

Case: The analgesic dosage was gradually increased (figure 1). Tylox was changed to Demerol 100 mg IM every four hours, then every three hours, and then Methadone, 5 mg by mouth every six hours was added. Pain still recurred before each analgesic dose so on day 4 the physician ordered "Demerol 100 mg IM or by mouth every two hours." Methadone was increased stepwise so that by day 7 the order read "10 mg by mouth every four hours." On day 7 the Demerol could be reduced to 100 mg IM every four hours. Some analgesics were ordered around the clock but others were ordered "p.r.n.," so nurses often withheld analgesics when the patient was vomiting or if he appeared to be asleep. During the hospitalization a total of 15,200 Analgesic Units were ordered, but only 9,307 were actually administered (61 percent).

An abdominal ultrasound showed that there were no liver metastases but the ascites was found to contain malignant cells. An oncologist felt that the patient did not have long to live and that he would not tolerate palliative chemotherapy. He was nauseated most of the time.

The doctors recorded the degree of his pain only three times: he was "in pain" on days 2 and 4, and pain was "controlled" at discharge. He was sent home on metoclopramide, 10 mg by mouth every four hours for nausea, Dilaudid, 2 mg by mouth every four to six hours and methadone 10 mg by mouth every four hours.

Figure 1. Pain medication, first admission: Each point represents the sum of Demerol and methadone ordered and administered each day, in Analgesic Units. (*One Analgesic Unit is the amount of analgesia provided by one mg of Demerol administered intramuscularly).

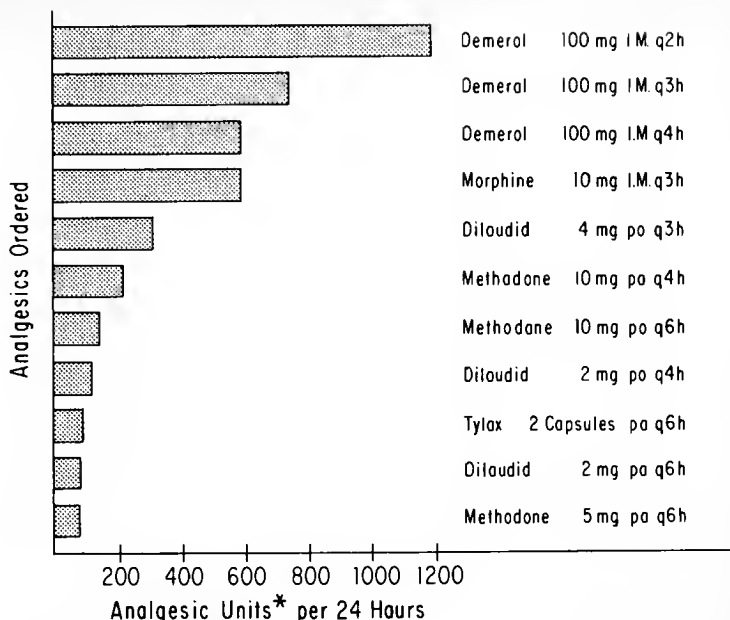


Instead of using trial and error, calculate equivalent doses when switching narcotics.

Comment: Clearly, our physicians, proceeding by trial and error, had a very difficult time controlling the patient's pain. They increased the dosage a little each day and took seven days to reach their maximum (figure 1). They also learned that in order to keep pain from recurring before each dose, the patient needed Demerol every two hours.

Some of the analgesic orders demonstrate the common difficulty in skillfully exchanging one analgesic regimen for another. For example, Tylox was ordered even though it is much less potent than the parenteral Demerol previously used at the other hospital. Furthermore, the order for Demerol, 100 mg IM or by mouth, makes no sense. Demerol by mouth has only one-third the analgesic potency of Demerol administered IM, and is not an equivalent alternative. Worst of all, the Dilaudid prescribed on the day of discharge (120 Analgesic Units per day, figure 2) was not nearly equivalent to the final Demerol dosage in use at the end of his hospitalization (600 Analgesic Units per day). After a long process of trial and error to find a satisfactory analgesic dose, the patient went home on less than half enough analgesic (figures 1 and 2).

Figure 2. Relative potency, over twenty-four hours, of analgesics: This figure shows all the narcotic orders that were written for this patient during his two admissions ("po" = by mouth, "q2h" = every two hours.) (*One Analgesic Unit is the amount of analgesia provided by 1 mg of Demerol administered intramuscularly.)



More Pain Management Strategies

5. Young patients require analgesics at short intervals.

Narcotics have a shorter duration of action in young patients. The duration of action of morphine in patients under age twenty-nine is about 2.5 hours, whereas it is nearly four hours in patients over age seventy.³ Demerol has an even shorter duration of action than morphine, so it should be prescribed at intervals of less than three hours and the patient should be checked frequently to see if pain recurs before the next dose.

Demerol relieved our patient's pain for only two hours. Although this may indicate that his hepatic function was good (he had no liver metastases), the patient also became more and more anxious because pain returned before each scheduled dose making his pain more difficult to relieve. To avoid analgesic peaks and valleys, it is better to give analgesics at frequent intervals or to use longer-acting narcotics whenever possible.

6. Use long-acting analgesics.

Several long-acting analgesics are available and have been used successfully to manage severe pain in terminal cancer; most of these can be given by mouth. The Brompton Cocktail (originally a solution of heroin, cocaine, chloroform water, alcohol and a flavoring agent) has become well known because British hospices have used it with great success. In this country, oral morphine solution is generally used and seems just as effective. It is long-acting when compared to parenteral Demerol, with a duration of action of four to five hours. It is consistently absorbed from the gastrointestinal tract, although larger

doses are required by mouth than parenterally. When used in doses of 20 to 120 mg five to six times a day, patients achieve good pain relief but experience transient drowsiness for the first 24 hours. Nausea and vomiting may also occur but can be treated by adding an antiemetic to the mixture. Since the solution is taken by mouth, patients can be treated at home.⁴ As an alternative, Methadone provides even longer analgesia (four to eight hours), is very cheap and can be administered by mouth or parenterally. Wide fluctuations of blood analgesic levels are avoided, preventing the potential complication of physiologic withdrawal in patients who require narcotics for weeks or months.

A distinct disadvantage of short-acting analgesics such as parenteral Demerol is that nurses can not always administer them on time. This may partially explain why our patient received only sixty-one percent of the narcotic Analgesic Units that were ordered. Unless there is an excellent nurse-patient ratio or the patient is attended by a family member at home, it is wise to prescribe a narcotic with a longer duration of action than Demerol.

7. Wake the patient if necessary.

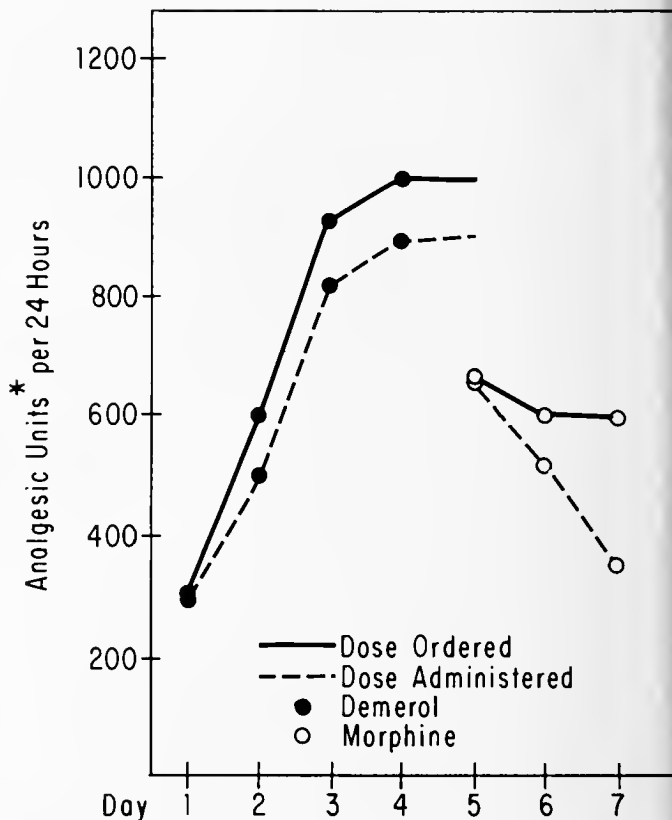
Most nurses will not wake patients to give analgesics, although they will wake them to give antibiotics or other drugs. Severe pain is more difficult to alleviate after an analgesic dose has been withheld. On several occasions when our patient's analgesics were withheld because he was sleeping, he woke to ask for them only thirty minutes to an hour later. It is better to give analgesics at fixed intervals around the clock to keep severe pain from recurring a short time later.

The patient was readmitted with severe pain.

Case: Three weeks later the patient was readmitted with ascites, edema and severe pain. His physicians made explicit plans to evaluate and treat the ascites and edema, but ordered Dilaudid, 2 mg, one to two tablets by mouth every three to six hours as needed for pain, and methadone, 10 mg by mouth every four hours around the clock. Dilaudid was never given. Although metaclopramide, 10 mg by mouth four times per day, was ordered for vomiting, nausea and vomiting continued and the patient could not retain the methadone. When pain control proved unsatisfactory, parenteral Demerol was started and the dose was rapidly increased to 100 mg IM every two hours (figure 3).

The patient continued to complain of severe pain so on day 4 Demerol was stopped and morphine, 10 mg IM every three hours, was begun. Parenteral vistaryl was given with each dose; afterwards the patient was more comfortable. He died three days later.

Figure 3. Pain medication, second admission: Each point represents the amount of Demerol or morphine ordered and administered each day, in Analgesic Units(*) (*One Analgesic Unit is the amount of analgesia provided by 1 mg of Demerol administered intramuscularly.).



Analgesic orders were vague.

Nausea and vomiting interfered with pain management.

The physicians went narcotic-shopping.

Comment: Again, the patient's primary physician failed to make a pain assessment or plan. The orders reflect this: the Dilaudid order was so broad that the analgesic decision was essentially delegated to the nurses. They could give him as much as two tablets every three hours (320 Analgesic Units daily, figure 2) or as little as one tablet every six hours (80 Analgesic Units daily). Even worse, because the order was "p.r.n.," the nurses also could have chosen to give no Dilaudid at all. That is what happened.

The Dilaudid order was worthless because Dilaudid was never given. Moreover, the methadone order was unsatisfactory because the patient was vomiting and could not take the drug by mouth. Vomiting was not controlled until a parenteral antiemetic was given round the clock.

When the patient was still in pain on Day 4, the physicians decided Demerol had "failed" and abandoned it. But since they did not calculate equivalent narcotic dosages they ordered a dose of morphine that was even less potent than the Demerol that had "failed." Fortunately, the patient became more comfortable during the last three days of his life, possibly because his nausea was controlled or because parenteral morphine has a slightly longer duration of action than Demerol.

More Pain Management Strategies

8. Take charge of pain management: Write clear analgesic orders.

A physician who writes narcotic orders that allow a wide discretionary range in dose and dosing interval essentially abdicates his or her responsibility to manage pain. The responsibility is left with the nurses, who rotate every eight hours, and who receive little training in pain management. There may be no primary nurse. Sometimes there are too few nurses on each shift to make good pain assessments and to administer analgesics frequently and promptly.

Pain is managed most successfully by someone who takes a firm leadership role, decides on a definite pain control plan, assesses the patient frequently and adjusts the regimen as needed. When there is a primary nurse skilled in pain management and there is a favorable nurse-patient ratio, the nurse can certainly assume a large part of this responsibility. But in many hospitals such ideal conditions do not exist. It is then better for the physician to take charge of pain management by writing clear analgesic orders that do not allow a discretionary range in dosage. Based on how much pain is relieved by each dose, and how long relief lasts, the physician should frequently adjust the amount of narcotic per dose and the interval between doses.

9. Control nausea and vomiting.

Many cancer patients are plagued by nausea and vomiting. Some patients have anticipatory vomiting on the day they are scheduled for chemotherapy. Nausea and vomiting can be caused by chemotherapeutic agents or by the tumor, especially if the tumor involves the stomach. Severe pain can cause nausea and vomiting. It is difficult for the nauseated patient to tolerate oral analgesics; therefore prescribe parenteral narcotics until these symptoms are under control. The patient may require parenteral antiemetics around the clock. Narcotics themselves stimulate the brainstem's chemoreceptor trigger zone and cause nausea and vomiting in some people. Although it can be difficult to sort out just what is causing a cancer patient's nausea, narcotic-induced nausea may resolve after several doses and it can generally be improved or prevented by lying in bed.

Standard antiemetics such as Compazine, Phenergan or Tigan may adequately control nausea and vomiting. These drugs are available in suppository and injectable preparations as well as in oral form. Antiemetic suppositories can be given around the clock to control persistent nausea and vomiting and are especially useful for outpatients or for patients who do not tolerate injections because of diminished muscle mass. The vomiting induced by chemotherapeutic agents, especially Cisplatin, Adriamycin and nitrogen mustard may be refractory to standard antiemetics; clinical trials using haloperidol, droperidol, cannabinoids and metoclopramide have shown that these may be somewhat more effective.⁵

10. Use oral analgesics.

Once nausea and vomiting have been controlled, the

patient should be started on oral analgesics. For over ten years, British hospices have reported that severe cancer pain can be controlled to the end or near the end of life with oral analgesics. Oral analgesic strategies fail most commonly because the oral regimen chosen provides many fewer Analgesic Units than the parenteral regimen had provided (figure 2). This problem can be avoided by calculating equivalent doses. When the patient has required large doses of parenteral narcotics, choose an oral analgesic such as morphine elixir or methadone; the dosage of Tylenol #3, Tylox or Percodan is limited because of the Tylenol or aspirin they contain. If dysphagia is present, morphine elixir may be easier to swallow than methadone tablets. After pain has been controlled with oral analgesics around the clock, the dose or dosing interval often can be decreased because anxiety and pain have decreased. After several days, methadone dosage may need to be reduced because tissue storage sites become saturated and half-life increases. This is especially true for patients with metastases to the liver or brain or with renal insufficiency. The patient will become sleepy or confused as methadone accumulates; this is best treated by withholding methadone for twelve hours then restarting it at a lower dose or longer dosing interval.⁶

Oral analgesics should be used for several reasons: They have a somewhat longer duration of action than parenteral narcotics and provide smoother analgesia because rapid swings in blood analgesic levels are avoided. Parenteral Demerol has such a short duration of action that swings in blood levels are especially pronounced. Oral analgesics spare patients from repeated painful injections, especially emaciated patients who have diminished muscle mass. Importantly, oral analgesics allow patients to go home and spend time with loved ones in a familiar environment. At home patients no longer have to compete for the attention of busy nurses and they or their family members can promptly administer pain medication as directed.

If the patient is unable to take medication by mouth, sometimes pain can still be managed at home by using analgesic suppositories. Dilaudid is available in 3 mg suppositories and pharmacists can prepare other narcotics in suppository form. Dilaudid by suppository provides 25 Analgesic Units per mg.

11. Don't go narcotic-shopping.

We often get angry at patients who shop from doctor to doctor and never stay with any treatment long enough to benefit from it. Doctors do the same thing when they switch analgesics, hoping that the new one will somehow be "stronger," "faster" or "better." Many people think morphine is "stronger" than Demerol, and that is apparently why our physicians switched to morphine when Demerol had not "worked" after four days. But morphine is not intrinsically "stronger" than Demerol; equivalent doses can be determined by calculating Analgesic Units (table 1). Any experienced physician knows that pain man-

agement is complex and that no single drug will make it simple. Doctors should never need to change narcotics out of blind desperation or a false hope that a "new" drug will be "better" when the real problem is incomplete assessment of patients, broad discretionary analgesic orders or drug administration schedules that allow too small a dose at too long an interval.

Summary

The American College of Physicians recognizes that internists need to learn more about narcotics and how to use them to treat severe, chronic pain in terminal cancer.¹ Pain control for these patients is a difficult but achievable goal. It is difficult because each patient is different; pain is not like pneumococcal pneumonia where a fixed dose of antibiotic will make most patients better. It is a time-consuming process because frequent patient assessment and regimen adjustments are required, but it is worthwhile because much suffering can be relieved. Physicians can learn to control pain by using several strategies to avoid common pitfalls (table 2).

The analgesic prescription for an individual patient must take into account the severity of pain, the patient's age, and whether the patient has nausea or vomiting. Determine the severity of pain through an accurate pain assessment: learn which analgesics have already been tried; use the information to make a pain control plan. Use palliative radiotherapy, chemotherapy or surgery when indicated and look for secondary complications such as pathologic fractures.

The primary physician should take charge of pain management and write precise analgesic orders. Most cancer patients will have better pain control if narcotics are given around the clock instead of "p.r.n.," because this prevents pain and anxiety from recurring before each analgesic dose. If necessary, wake the patient to give analgesics on schedule. Choose long-acting analgesics, especially when liver and kidney function is good and when the patient is young. Control nausea and vomiting.

Become skilled in switching narcotics or routes of administration by learning to calculate Analgesic Units using table 1. This is the key to using narcotic analgesics proficiently. One doesn't need to hop arbitrarily from narcotic to narcotic. One analgesic is not "stronger" than another, but some narcotics are traditionally prescribed at doses that deliver more Analgesic Units than others. Even morphine, which many physicians believe is not effective when given

Table 2
Strategies for Using Narcotics to Control Severe, Chronic Pain in Terminal Cancer

Make a pain assessment
Make a pain control plan
Take charge of pain management
Write precise analgesic orders
Calculate Analgesic Units
Switch drugs using equivalent doses
Avoid "p.r.n." dosing
Wake the patient if necessary
Use long-acting analgesics
Use short intervals for young patients
Control nausea and vomiting
Use oral analgesics
Don't go narcotic shopping

by mouth, can provide good analgesia if enough is given to make up for decreased gastrointestinal absorption. High narcotic doses may be required to achieve pain relief; the doctor will need to monitor these patients closely for side effects such as constipation and confusion. By calculating Analgesic Units, it is possible to avoid lowering your patient's analgesic dosage inadvertently when you must change from one narcotic to another.

Above all, it is never appropriate to withhold adequate doses of analgesics out of a misplaced fear of narcotic addiction. When curative therapy has failed, pain management is the most important thing the physician can offer a cancer patient, remembering his or her duty to cure only sometimes, but to comfort always.

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The Clinical Management of Sore Throat: A Comparison of Three Ambulatory Settings

Michael S. O'Malley, M.S.P.H., John J. Frey, M.D., and Axalla J. Hoole, M.D.

SORE THROAT is a common patient complaint, but its proper management is still a matter of debate. Respiratory infections, many of which present with a sore throat, are the number one cause of acute illness in the U.S. and sore throat is the fourth most common symptom presenting to medicine practices in the U.S.¹⁻² Few acute respiratory diseases can be treated and fewer still have important long term morbidity. Streptococcal pharyngitis, however, is both treatable and a precursor to acute rheumatic fever. The diagnosis and treatment of streptococcal pharyngitis is an occasion for the continuing debate over the clinical management of sore throat.

In the past, medical opinion has urged the culturing of all patients presenting with a sore throat and the treatment of all positive cultures with antibiotics as the best means for minimizing the risk of rheumatic fever.³ Recent studies have recommended different culture and treatment strategies. In a study of the families of children with rheumatic fever, Peter and Smith proposed throat cultures for children with predominant sore throat symptoms and a temperature of 37.3°C or greater.⁴ Forsyth suggested a cluster of symptoms (fever, exudative pharyngitis, cervical adenitis) as a clinical guide, reserving throat culture only in patients at high risk for acute rheumatic fever. This approach provided a combination of accurate case finding and rational use of laboratory services.⁵ Tompkins, Burnes and Cable have outlined three culture-treatment strategies for endemic pharyngitis based upon the percentage recovery of bacillus from the cultures.⁶ These conflicting opinions have prompted one author to conclude that "there are no firm guidelines for culturing."⁷

Given that the normative models (what physicians *should* be doing) lack consensus, what *are* physicians doing when patients present with a sore throat? To answer that question, we observed the clinical management of sore throat at three different ambulatory care sites — a Family Practice Center, a Pediatric Screening clinic, and a general medicine Walk-In clinic — in a university teaching hospital.

Methods

The setting for this study was the North Carolina Memorial Hospital, a public teaching and referral hospital in Chapel Hill, North Carolina. At NC Memorial, the Family Practice Center sees patients of all ages for both acute and chronic problems. Faculty and residents from the Department of Family Medicine comprise the Center's physician staff. In 1981-82, 16,041 patients were seen in the Center.

The Pediatric Screening clinic provides round-the-clock consultations for unscheduled patients aged one month to 16 years. In 1981-82, the faculty attendings and the resident staff from the Department of Pediatrics saw 8,349 patients. The Walk-In clinic sees unscheduled adult patients on weekdays for non-emergent medical complaints. The staff consists of second year residents from the Department of Medicine under the supervision of a faculty attending physician. Patient visits during 1981-82 numbered 6,138.

The data for this study were drawn from patients visiting the Family Practice Center in March 1982 and from patients attending the Pediatric Screening and Walk-In clinics in December 1981 and January 1982. To be eligible for the study, patients either had to be making a first visit for a problem that included a complaint of a sore throat or had to be making an initial visit for a problem that led to the ordering of a throat culture. A "sore throat" included complaints of "scratchy," "dry," "irritated" and other common manifestations of an infected or swollen throat.

Origins of the study sample are summarized in figure 1. During the month of data collection, the Family Practice Center had 1,629 patient visits. A presenting complaint log and a record of all cultures identified 88 eligible patient visits (5%). Four patients' records were unobtainable, reducing the final Family Practice Center sample to 84 encounters (95% of eligible).

In Pediatric Screening, log books of patients' presenting complaints and lab cultures identified as eligible 142 (11%) of the total 1,254 patient visits during the two month study period. To equalize sample sizes by clinic location, a random 50% sample of all eligible patient visits ($n = 69$) was selected for inclusion in the study.

During the two month study period, 1,035 visits took place in the Walk-In clinic, but records for review were available for only 879 (84%) of the encounters. Of this number, 70 (8%) met the study criteria.

From the Departments of Medicine and Family Medicine, School of Medicine, University of North Carolina, Chapel Hill 27514.

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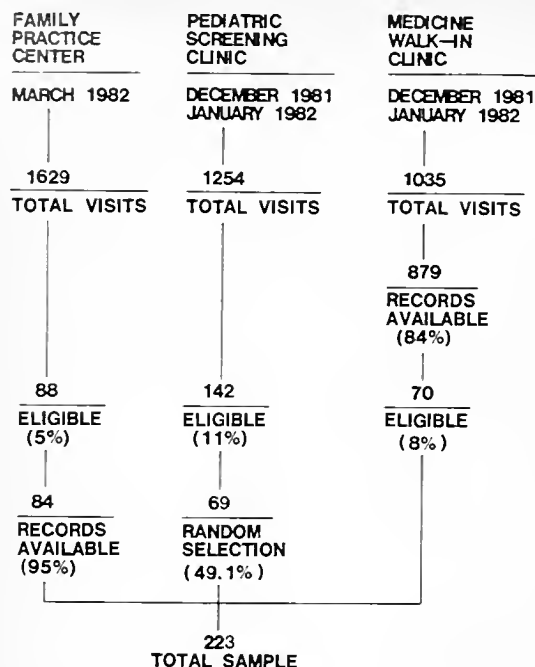


Figure 1

Total sample size for the study, then, was 223 patient visits representing 74% of all patient visits eligible for the study.

The medical records of all 223 study patients were reviewed for demographic and clinical information for the encounter of interest. Patients who were between four and 30 years of age (inclusive) were classified as "at risk" for rheumatic fever due to age. Clinical variables fell into three categories. (1) Presentation data included symptoms, expo-

sure to strep throat and physical findings (erythema, exudate, tonsillar enlargement and cervical adenopathy). (2) Management data included information about throat cultures (obtained/results), treatment (if/when/with what), and follow-up. (3) Physician data indicated the physician's diagnosis.

Results

Patients presenting with sore throat to the three different settings were somewhat dissimilar (table 1). Pediatric patients more often presented with a sore throat. Family Practice patients lived closer to the hospital and were more often white than were the patients of the other two settings.

Family physicians cultured virtually every patient (81/83, 98%) who presented with a sore throat. Eight of the cultures proved to be positive (figure 2). Pediatricians also ordered cultures on a high percentage of patient encounters (61 of 69, 88%), but nearly half (29/61, 48%) were positive for streptococcus A. Internists in the Walk-In clinic cultured only about half (36/70) of the patients with sore throat presentation. Only three of these cultures were positive.

Differences in cultures obtained appeared to be related to the patient's symptoms (table 2). Among patients whose major symptom was only a sore throat, physicians from all settings ordered throat cultures in a high percentage of patients. However, when the sore throat was accompanied by other symptoms, especially those suggesting upper respiratory problems, internists ordered throat cultures about half as often as pediatricians and family physicians, even among patients considered to be at risk by age for rheumatic fever.

Treatment of patients with a presentation of sore throat also differed across the three settings (table 3). In the Walk-In clinic, where cultures were done least often, internists treated nine of 33 (27%) patients without cultures and seven of 33 (21%) patients with negative cultures. In Pediatric Screening, where almost all patients were cultured, three of eight patients (38%) without culture and four

Table 1
Characteristics of Patients Presenting with
Sore Throat at Three Different Ambulatory Settings

Percent of Visits With Sore Throat Presentation	Family Practice Center (n = 84) 5%		Pediatric Screening (n = 69) 11%		Medicine Walk-In (n = 70) 8%	
	n	%	n	%	n	%
Race:						
Non-white	12	14	35	51	42	60
White	72	86	34	49	28	40
Gender:						
Male	35	41	34	49	22	31
Female	49	59	35	51	48	69
Age:						
Median		21		8		27
Range		3-77		2-38		16-77
At Risk (4-30)	58	69	58	84	43	61
Distance from Setting*						
≤30 minutes	79	94	48	71	43	62
>30 minutes	5	6	20	29	26	38

* One case missing for Medicine Walk-In and Pediatric Screening.

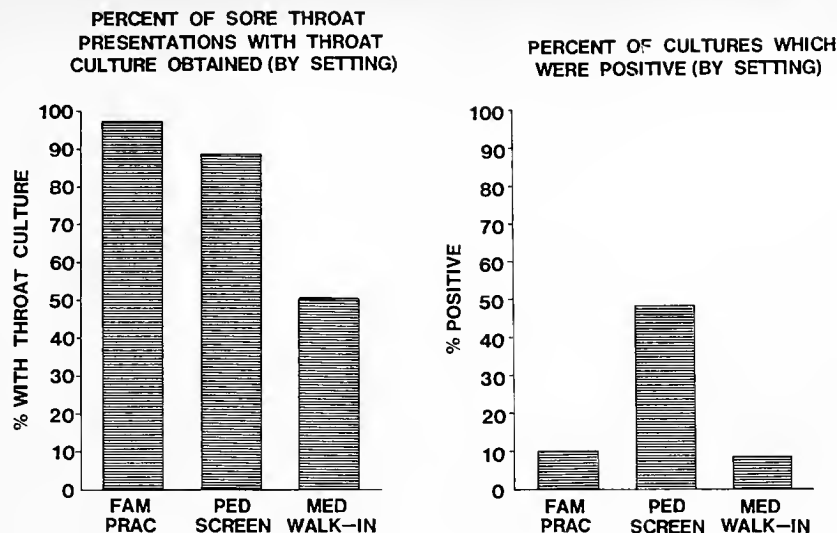


Figure 2

Table 2
Throat Cultures Obtained by Presenting Symptoms and Age Risk
At Three Different Ambulatory Settings*

Symptoms:	Family Practice Center			Pediatric Screening			Medicine Walk-In		
	pts	n	%	pts	n	%	pts	n	%
Sore Throat Only									
At Risk Patients	13	13	100	13	10	77	9	8	89
All Patients	19	19	100	13	10	77	10	8	80
Sore Throat and URI									
At Risk Patients	27	25	93	17	14	82	24	11	46
Not At Risk Patients	38	36	95	21	17	81	39	15	38
Sore Throat and Other Symptoms									
At Risk Patients	6	6	100	13	13	100	8	5	63
Not at Risk Patients	9	9	100	14	14	100	18	10	56

* Missing from this table are those cases where there was evidence of a lab test but where no record of the clinic note (for symptom description) was available.

Table 3
Antibiotic Treatment of Patients By Throat Culture
In Three Different Ambulatory Settings

Throat Culture:	Family Practice Center		Pediatric Screening		Medicine Walk-In	
	n	%	n	%	n	%
No Culture Obtained						
Total Patients	2	100	8	100	33	100
Treated	0	0	3	38	9	27
Not Treated	2	100	5	62	24	73
Positive Throat Culture						
Total Patients	7	100	29	100	3	100
Treated	5	71	22	76	2	67
Not Treated	2	29	7	24	1	33
Negative Throat Culture						
Total Patients	69	100	28	100	33	100
Treated	24	35	4	14	7	21
Not Treated	45	65	24	56	26	79

Table 4

Point of Treatment for Patients Suspected of Strep Throat Across Three Different Ambulatory Settings

	Family Practice Center		Pediatric Screening		Medicine Walk-In	
	n	%	n	%	n	%
Patients with Throat Cultures Obtained	36	100	57	100	76	100
Total Patients Treated with Antibiotics	9	25	26	46	29	38
Treated with Antibiotics on First Visit	9	100	8	31	24	83
Treated with Antibiotics on Follow-up Visit (2-3 days)	0	0	18	69	5	7

of 28 patients (14%) with negative cultures were treated with antibiotics. Family physicians did not treat either of the two patients without a throat culture, but they did treat 24 of the 69 patients who had a negative culture. In a few cases, treatment included antibiotics prescribed for other concurrent infections (e.g., otitis media or sinusitis).

According to the medical records a number of patients with positive cultures from all settings did not receive antibiotic treatment (table 3). Pediatric Screening had the highest rate of untreated positives, 24% (7/29). Given the overall occurrence of sore throat presentation in the Pediatric Screening Clinic and the occurrence of untreated positives, it would follow that 12 out of every 1,000 patient visits would result in an untreated streptococcal infection.

For patients with throat cultures, pediatricians more often opted for a delayed treatment strategy than did the physicians in the other two settings (table 4). Of the 36 Walk-In patients with throat cultures, nine (25%) were treated, all on the initial visit. Family physicians more often treated patients with cultures (29/76, 38%), but again the vast majority were treated on the initial visit (24/29, 83%). In Pediatric Screening, on the other hand, 26 of 57 (46%) patients with cultures were treated, but only 8 of the 26 (31%) received treatment on the first visit.

Discussion

Observed management of sore throat in a university teaching hospital very much reflected the current debate over the normative management of sore throat. Physicians in three ambulatory care settings had different approaches to the problems of culture and treatment.

This study has several limitations. First, the small sample size did not permit comparisons of treatment strategies across all three settings while controlling for risk factors, cultures (degree of positivity), presenting symptoms and physical findings. Second, because physicians do not always record all of their activities, written medical records (charts, logbooks) conservatively measure physician activity and generally overestimate omissions in care, such as failure to treat patients with positive throat cultures. Finally, sore throat symptoms, throat culturing, and streptococcal pharyngitis are subject to seasonal fluctuations with peaks in the winter months. The data for this study were taken from cases appearing in peak months: December, January and March. Clinical management of sore throat may differ in other months of the year. Nonetheless, these data do suggest that in actual practice, physicians disagree on the proper management of sore throat.

In this study family physicians and pediatricians cultured almost every patient presenting with a sore throat while internists cultured more selectively. This strategy may be fairly common. In a 1978 survey, Gillette found that 66% of family practice residency programs used throat cultures in managing adult patient sore throats, while only 36% of practicing physicians did so.⁸ A recent statewide study in Rhode Island estimated that approximately 50% of all physicians cultured every sore throat presentation, and that about 70% of all patients with a sore throat were cultured.⁹ In the same study, pediatricians cultured more often than did non-pediatricians, but there was no reported difference between internists and family physicians.

Once a culture was obtained, family physicians and internists were equally likely to treat the patient without a culture result. Pediatricians were more likely to postpone treatment until the results were known. By contrast, in the Rhode Island study, pediatricians were more likely to treat on the initial visit, although the vast majority (87%) of all physicians reported likely initial visit treatments.⁹

None of the physician groups in this study closely followed the normative management model suggested by Tompkins et al.⁶ Family physicians adopted a strategy of culture and treat on the first visit, a practice that may have generated additional costs. A similar pattern has been found among Emergency Room physicians.¹⁰ Internists, who more selectively cultured and treated, tended toward Tompkins' strategy C (neither culture nor treat), perhaps following guidelines for management based upon physical findings.¹²⁻¹⁵ Pediatricians, however, appeared to have adopted a strategy completely opposite to that proposed by Tompkins. Whereas the 48% positive throat culture rate in the Pediatric Screening clinic would have suggested to Tompkins that patients should be treated without culture, pediatricians cultured almost all patients and then treated all positive cultures.

The cost implications for the patient (time and travel) likely vary from setting to setting and should have some influence upon the physician's selection of a management strategy. For example, in the Family Practice Center where the vast majority (94%) of the patients live within 30 minutes of the clinic and where the positive culture rate is relatively low (10%), a strategy of a return visit treatment based upon a culture result would seem appropriate. On the other hand, in Pediatric Screening, where a larger percentage of the patients come from further away (29% more than 30 minutes), where the positivity rate is much higher (48%), and where compliance with oral antibiotics is likely

ow, a more appropriate strategy would seem to be treatment on the initial visit, especially in those cases falling into high risk categories defined by age, exposure, symptoms and physical findings. Pantell's multi-factorial analysis of seven different strategies for managing sore throat supports this selective, population-specific approach on a cost effective basis.¹¹

Debate over the proper management of sore throat is not just a tempest in academic medicine's teapot. Traditionally, the principal aim of sore throat management has been to identify and treat streptococcal pharyngitis so that it will not later develop into a more serious disease, such as acute rheumatic fever. However, acute rheumatic fever is no longer the scourge it once was. Twenty years ago, Gorlis et al estimated the incidence of new acute rheumatic fever to be 24 cases per 100,000. More recent studies in metropolitan Memphis, Tennessee and in Rhode Island have reported much lower incidence rates: .64 per 100,000 and .2 per 100,000 respectively.^{9, 16} This decline in acute rheumatic fever actually became apparent prior to the widespread introduction of antibiotics. Thus, while the treatment of streptococcal pharyngitis has surely contributed to the continuing decline in acute rheumatic fever, the extent of that contribution is unknown. Further, although the direct costs of culture and treatment are relatively small for any one patient, the accumulated nationwide costs are quite substantial. Serious questions exist about the cost-effectiveness of culturing and treating sore throats.

This study took place in a university teaching hospital among physicians with a variety of clinical experiences. Life-long practice habits are likely formed in these training settings, most often with residents adopting the normative behaviors demonstrated by the senior faculty. Although management of sore throat within each of the three settings observed showed internal consistency, none of these reflected either medically optimal or cost-effective patterns

of management. Particularly in an era of increasing cost consciousness, teaching centers must focus on both these factors if future primary physicians are to be trained to function effectively. Given that physicians currently do not agree, in either a de facto or a de jure sense, on the proper management of sore throat, a comprehensive reappraisal of this aspect of clinical medicine is in order.

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Thrombolytic Therapy

Julie Jacobs

Dear Readers:

The Duke Medical Center Pharmacy will publish reviews of therapeutic agents commonly prescribed within the hospital setting in the form of a special column for the North Carolina Medical Journal. These reviews, written by pharmacy residents and clinical pharmacists, are regularly published in the Duke Hospital Drug Information Bulletin. Each is reviewed by staff physicians with expertise in the area each article addresses. The editors welcome reader comments and suggestions.

Christine C. Rudd, Pharm. D.
Richard Drew

THROMBOLYTIC therapy represents a new medical approach to the treatment of patients with thromboembolic diseases. Conventional anticoagulant therapy with heparin or coumarin derivatives does not bring about the dissolution of thrombi and emboli. A lysis of clots would permit a return of blood flow through the affected vessels and reduce the pain and swelling associated with the destruction of venous valves in patients with deep venous thrombosis. Thrombolytic therapy may be of benefit in decreasing the long-lasting ill effects associated with thrombosis and embolism. It in no way replaces or minimizes the use of anticoagulants for the continued care of such patients, but offers an alternative approach with considerable advantages in terms of long-range prognosis for such diseases.

Two thrombolytic agents are available in the United States for clinical use. Streptokinase is marketed as Streptase (Hoeschst-Roussel Pharmaceuticals, Inc.) and Kabikinase (Kabi Group). Urokinase is marketed as Abbokinase (Abbott Laboratory) and Breokinase (Breon Labs).

Streptokinase was discovered in 1933 by Tillett and Garner when they observed that a filtrate of Group C beta-hemolytic streptococci lysed a human plasma clot.¹ Subsequent studies helped to characterize the interaction of the extract with the fibrinolytic system and showed that the activator substance acted on plasminogen to produce plasmin, an active enzyme.² This activator was named "streptokinase." In 1959, Johnson and McCarty successfully lysed thrombi that had been experimentally induced in forearm veins of volunteers.³

MacFarlane and Pilling isolated a similar substance from human urine in 1946.⁴ This substance was given the name "urokinase" by Sobel and his colleagues.⁵ Further investigations demonstrated that urokinase was also a plasminogen activator. Sherry et al. subsequently provided important pharmacologic and clinical information that led to the experimental use of urokinase for therapeutic thrombo-

lysis.⁶ By 1960, Ploug and Kjeldgaard had developed purification methods for isolation of urokinase from urine in a form suitable for clinical investigations.⁷ This urokinase possessed high specific activity; it was free of contamination and was also virus-inactivated, nontoxic, and nonpyrogenic.

Mechanism of Action

While heparin has no direct effect on formed thrombi, streptokinase and urokinase actually promote dissolution of a thrombus by stimulating the conversion of fibrin-bound inactive proenzyme plasminogen to active enzyme plasmin, where it is protected from circulating inhibitors (see figure 1). Streptokinase does this indirectly by forming an activator complex with plasminogen, while urokinase acts directly.⁸⁻¹⁰ Plasmin is a proteolytic enzyme that acts in two areas. Locally, it promotes fibrin digestion, resulting in dissolution of the thrombus.⁸⁻¹⁰ Systematically, biochemical changes in the blood result in a "lytic state" which can be defined as a decrease in plasma plasminogen and fibrinogen, and a prolonged prothrombin or thrombin time, thus increasing the potential for hemorrhage.⁸⁻¹⁰ Natural protein inhibitors (solid cross bars, figure 1) of activation are overcome during the induction of the lytic state of infused activators because the amount of drug used in standard treatment regimens far exceeds the inhibiting potential of these proteins.¹¹

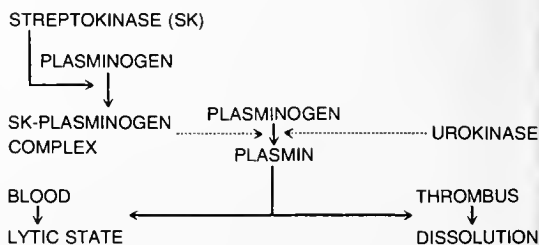


Figure 1.¹¹ Action of Streptokinase and Urokinase in achieving thrombolysis.

From the Department of Pharmacy, Duke University Medical Center, Durham 27710.

Pharmacokinetics

The plasma clearance rates of streptokinase have been studied in both normal and immune man.¹² Intravenously injected streptokinase is cleared from the circulation at two distinct rates. The "fast" rate (18 minutes) appears to be a consequence of the combination of streptococcal antigen with its antibody and the subsequent clearance of this complex.¹² The "slow" rate (83 minutes) occurs in the absence of plasma antibody and may be due to activity of the reticuloendothelial system.¹² The fibrinolytic effect disappears within a few hours after discontinuation of the infusion, but prolonged thrombin time may persist for 12-29 hours because of a decrease in plasma levels of fibrinogen and an increase in the amount of circulating fibrinogen degradation products.¹³

Following intravenous administration, urokinase has a circulating half-life of 20 minutes or less.¹⁴ As with streptokinase, fibrinolytic activity may persist for 12-24 hours after discontinuation of the infusion.¹⁴

Kinetic data concerning the use of these agents in patients with renal or hepatic disease are unavailable because of the relative contraindications to their use in this population.

Therapeutic Uses

The clinical indications of thrombolytic therapy have been defined by the Food and Drug Administration. On the basis of results from clinical investigations, streptokinase has been approved for treatment of the following conditions: acute pulmonary embolism and deep-vein thrombosis (within seven days of onset of symptoms), arterial thrombosis, acute myocardial infarction, and occlusion of access shunts and intravascular or cavity catheters.¹⁵ Urokinase may be used in cases of acute pulmonary embolism (within seven days of onset of symptoms) and occlusion of access shunts and intravascular or cavity catheters.¹⁴

Most clinical studies have employed similar methodologies; thrombolytic agents have been administered into a peripheral vein or directly into the pulmonary artery and continued for 12 to 72 hours. Heparin has also been given for five to seven days followed by oral warfarin therapy. Many of the studies also included a control group treated with heparin only in conventional doses. Diagnosis of pulmonary embolism was most often confirmed by pulmonary angiography and lung scans. In most trials, improvement was measured by the mean reduction in clot size in the post-infusion angiogram compared with the preinfusion angiogram.

Pulmonary Embolism

Both streptokinase and urokinase have undergone extensive clinical evaluation in the treatment of pulmonary embolism in Europe and the USA in the past decade. Most of the early studies were uncontrolled and/or nonrandomized; therefore an accurate comparison between heparin and thrombolytic agents was not available. The most significant data comparing these two agents with heparin in the treatment of pulmonary embolism were produced by two large multicenters' randomized studies sponsored by the National Heart and Lung Institute (NHLI), the Urokinase Pulmonary Embolism Trial (UPET) and the Phase II Uroki-

nase-Streptokinase Pulmonary Embolism Trial.^{16, 17}

Phase I of this trial compared heparin with urokinase therapy in 160 patients with angiographically demonstrated pulmonary embolism.¹⁶ A well-documented clinical episode suggesting that pulmonary embolism had occurred within five days of the institution of therapy was necessary for patient eligibility. Patients receiving urokinase were given a loading dose of 2,000 CTA (Committee on Thrombolytic Agents) units/lb of body weight followed by 2,000 CTA units/lb/hr, while the patients given heparin received a loading dose of 75 units of heparin/lb of body weight followed by 10 units/lb/hr for a total of 12 hours. After termination of the 12-hour infusion, all patients received heparin intravenously for a minimum of five days followed by orally administered warfarin therapy. Urokinase was found to be significantly superior to heparin in accelerating the resolution of pulmonary embolism. Especially important was the fact that patients with massive pulmonary embolism accompanied by shock had the greatest degree of resolution ranging from 33.4 to 68.6 percent. However, the two-week mortality rate for both regimens was approximately equal.

Phase II of this trial sought to determine whether 24 hours of urokinase increased the amount of clot resolution beyond that found after 12 hours and how 24 hours of streptokinase compared with 24 hours of urokinase.¹⁷ The eligibility criteria for admission of patients into this trial were very similar to those established in the Phase I trial. Patients receiving streptokinase were administered a loading dose of 250,000 units of streptokinase intravenously over 20-30 minutes, followed by 100,000 units/hr by a constant infusion pump for 24 hours. Patients given urokinase received a loading dose of 2,000 CTA units/lb/hr for either 12 or 24 hours. After termination of each infusion, all patients received heparin intravenously for a minimum of five days, followed by oral doses of anticoagulants. The mean improvement in pulmonary arteriogram and hemodynamic variables, as well as the incidence of hemorrhagic complications and recurrence of pulmonary embolism, was not significantly different among treatment groups. The two-week and six-week mortality rates also were not significantly different. Thus the data from this trial indicate no further benefit from 24 hours of urokinase than with 12 hours and suggest that the efficacy of urokinase and streptokinase is similar.

In a recently published report, Sharma et al. selected 40 patients from the NHLI studies and observed the effects of thrombolytic agents on small peripheral pulmonary clots that were beyond the resolving capabilities of angiography or scanning.¹⁸ Pulmonary capillary blood volume and total diffusing capacity of the lung remained unchanged in the heparin group, but improved significantly in the thrombolytic group at two weeks and one year.

A study by Tibbitt et al. compared streptokinase with heparin therapy in 30 patients with life-threatening pulmonary embolism.¹⁹ Two patients in the streptokinase group and five in the heparin group were excluded because they failed to complete 72 hours of therapy. In mean angiographic scores, response to treatment was clearly better with streptokinase. The heparin group, however, consisted of a greater number of severely ill patients. A six-month

Table 1¹³

Summary of Clinical Trials Utilizing Urokinase, Streptokinase, and Heparin in Pulmonary Embolism

Reference/Study Design	Number of Patients	Drug	Mean Lung Scan Resolution (%)	Angiography (mean decrease in size of clots-%)	Mortality (%)
Co-op study ¹⁶	160	Urokinase	22.1		7.4
randomized, controlled		Heparin	8.1		8.9
Co-op study ¹⁷	167	Urokinase × 24h	29.2		9.0
randomized, controlled		Urokinase × 12h	20.0		9.0
		Streptokinase × 24h	18.5		9.0
Tibbitt et al ¹⁹	23	Streptokinase		61.0	0
randomized, controlled		Heparin		15.0	8.0
Ly et al ²²	20	Streptokinase		52.3	0
randomized, controlled		Heparin		20.6	20.0

followup revealed no significant differences between treatment groups in angiographic scores and pulmonary arterial pressures.

In an attempt to decrease costs and lower hemorrhagic complications, Edwards treated nine consecutive patients suffering massive embolism and shock with a low dose of urokinase (200,000-300,000) infused over two hours followed by heparin 10,000 U IV q4h.²⁰ The urokinase was infused directly into the pulmonary artery and provided rapid clinical improvement with clot lysis and no hemorrhage. Six of the nine patients had recurring pulmonary embolism, however, with death resulting in two.

Through a retrospective review of 68 patients with acute pulmonary embolism, Miller et al. evaluated the rate of treatment failures and mortality in shock versus nonshock patients treated with heparin, streptokinase, or embolectomy as primary therapy.²¹ The observation was made that when heparin was used as primary therapy, there were a greater number of total deaths and failures (50%) than with either streptokinase or embolectomy (25%).

In a controlled trial by Ly et al, patients with major pulmonary embolism were allocated randomly to receive streptokinase or heparin.²² The angiographic evidence of thrombolysis was significantly greater in the streptokinase group ($P < 0.01$). Two deaths were reported in the heparin group, one from massive embolism 15 hours after the start of treatment and the other four weeks later from a cerebral glioblastoma. In the streptokinase group, one patient died from a thrombotic occlusion of the inferior vena cava three weeks after treatment.

A summary of the major clinical trials utilizing urokinase, streptokinase, and heparin for pulmonary embolism appears in table 1.

Deep Vein Thrombosis

The rapid lysis of thrombi in the deep veins by streptokinase tends to preserve the anatomy and function of the venous valve cusps, whereas the slow resolution of thrombi with heparin therapy seems to permit distortion and destruction of the valves.²³ In the studies reviewed, streptokinase was generally used in the recommended doses for 72 hours in patients with less than two weeks' duration of symptoms. Venography was used in most cases to assess the decrease in blood flow due to emboli and to observe the

results of heparin or thrombolytic therapy. Analysis of study results revealed that thrombolysis was significantly greater with streptokinase, with complete lysis occurring in 30% of patients and substantial lysis in 65%.²⁴⁻²⁹ Patients receiving heparin therapy experienced less than a 10% lysis.²⁴⁻²⁹ The incidence of pulmonary embolism was approximately the same for both groups.^{24, 26-28, 30}

Seaman et al studied 50 patients and found that the degree of thrombolysis was significantly greater in the streptokinase-treated patients than in the heparin-treated patients ($P < 0.05$) after three days, although after ten days the difference decreased to a non-significant level.³¹ Common et al observed that in patients with more extensive disease, when either heparin or streptokinase is started later than the third day of onset, the usual result is healing by recanalization without valve preservation. Both Dhall et al and Tsapogas et al suggested that successful therapy correlated with initially low fibrinogen levels and substantially decreased levels after 24 hours.^{25, 30} Duckert et al and Watz et al noted that thrombolytic therapy was most effective when the thrombosis was located in the proximal rather than in the calf veins.^{27, 28}

The incidence of post-thrombotic syndrome was also examined in several studies. Common et al evaluated patients with similar distributions of clot severity after a mean of seven months.²³ Normal venograms were found in 40% of the streptokinase group but only 8% of the heparin group. In a study by Elliott et al, only one of the 17 patients who achieved 80-100% lysis with streptokinase developed postphlebotic symptoms, whereas only two of the 25 patients treated with heparin were found to have asymptomatic legs on followup.²⁶ No significant lysis was achieved in any of the 25 patients treated with heparin.

A summary of the major clinical trials using streptokinase and heparin in deep vein thrombosis appears in table 2.

Arterial Thrombosis and Embolism

In a small number of studies, streptokinase has been used successfully in the treatment of acute arterial thrombi and emboli. In 1974, Dotter et al reported their development of a selective-delivery, low-dose technique that concentrated the therapeutic action of streptokinase where it was needed.⁴⁹ In their series of 17 patients, indwelling selective catheters were used to perfuse streptokinase just above or

Table 2.
Summary of Clinical Trials Utilizing Streptokinase and Heparin in Deep Vein Thrombosis

Reference/Study Design	Number of Patients	Drug	Venography (%)	Morbidity (%)
Common et al ²³ randomized, follow-up	27	Streptokinase	(at mean, seven months) normal venogram (40) segmental venogram (6) complete recanalization (26) partial recanalization (26)	swelling (33)
		Heparin	normal venogram (8) segmental venogram (8) complete recanalization (58) partial recanalization (26)	swelling (50)
Elliott et al ²⁶ controlled, randomized	51	Streptokinase	80-100% (74) partial lysis (9)	(0)
		Heparin	no significant lysis (8) extension of thrombosis (8)	(8)
Duckett et al ²⁷ controlled, nonrandomized	145	Streptokinase	complete lysis (42) partial lysis (25)	pulmonary embolism (7.5)
		Heparin	complete lysis (0) partial lysis (10)	pulmonary embolism (12)
Watz et al ²⁸	35	Streptokinase	at 24 hrs-complete lysis (44) at 1-2 months-complete or partial lysis (66)	high valvular function (91)
		Heparin	at 24 hrs-complete lysis (6) at 1-2 months-complete or partial lysis (35)	high valvular function (13)
Tsapogas et al ³⁰ controlled, randomized	34	Streptokinase	complete or partial lysis (53)	(0)
		Heparin	complete or partial lysis (9)	pulmonary embolism (9)

directly into obstructing intra-arterial thromboemboli. Fresh clots readily dissolved with doses as low as 1/100th of those given intravenously to cause a therapeutic systemic hyperlytic state. A marked concomitant reduction in distant bleeding was also achieved.

While conducting a prospective, randomized, single-blind comparison of streptokinase with heparin therapy in 17 patients, Reichle et al found that total limb salvage was possible in 72% of the patients who received streptokinase compared with only 33% of the patients treated with heparin.³²

In another prospective, uncontrolled study conducted by Martin and involving 600 patients, streptokinase produced a clearance of femoral and ileac occlusions in 75% of the patients with symptoms of less than two weeks duration.³³ The reocclusion rates of ileac arteries averaged from 0-12%, however, while the femoral artery reocclusion rate approximated 50% at the end of the third year.

Totty et al investigated the use of low-dose fibrinolytic agents administered via an indwelling angiographic catheter in 22 patients with intravascular thrombi.⁵⁰ Thirteen perfusions were performed in association with 10 percutaneous transluminal angioplasty procedures. Of these, eight produced complete or nearly complete lysis of radiographically visible thrombi, while five brought about only partial lysis. Thirteen infusions were also performed in 12 patients who presented with acute or subacute vascular thrombosis and were not considered candidates for angio-

plasty. Partial lysis was seen in all but one of the patients with spontaneous thrombosis; however, no patient had complete lysis.

In a recent study conducted by Berni et al, successful thrombolysis was achieved in 12 of 16 arterial occlusions (75%) following intra-arterial infusion of streptokinase at a dosage of 5,000 U per hour.⁵¹ All 16 of the occlusions were classified as being acute on the basis of a sudden development of ischemic symptoms within two weeks before the initiation of therapy. The incidence of successful lysis was similar in embolic occlusions (80%) and thrombotic occlusions (70%). The time interval from the onset of symptoms to the initiation of treatment ranged from 2 hours to 10 days, which approximates the age of the clot or thrombus. Lysis occurred in 78% of the occlusions treated within 24 hours compared with 71% in those of longer duration. Therefore, neither the etiology nor the duration of the occlusion influenced the ability to achieve effective thrombolysis.

Low-dose intra-arterial streptokinase therapy appears to be an effective alternative in the treatment of thromboemboli producing acute arterial occlusion. The major limitations of thrombolytic therapy are the time interval required to ensure complete thrombolysis and preserve the viability of the limb. Although low-dose intra-arterial streptokinase appears to be associated with a decrease in the incidence of hemorrhagic complications, hypofibrinogenemia and bleeding abnormalities continue to be a problem.

Acute Myocardial Infarction

Several multicenter studies have used intravenous streptokinase in the treatment of acute myocardial infarction. The rationale was that the size of the infarct might be reduced by prevention of thrombosis in small vessels at the periphery of the infarct. Controlled trials in both the United Kingdom and Australia evaluated several hundred patients but were unable to demonstrate a significant decrease in mortality compared with placebo or other anticoagulants.^{34, 35} However, patients were entered into these trials up to 72 hours following the onset of symptoms. In the European cooperative trial, a decrease in mortality from 30.6% to 15.6% within six months was demonstrated with streptokinase compared with placebo when initiation of therapy took place within 12 hours of onset of symptoms. Only 13.5% of all patients with myocardial infarction, however, were included in the study.³⁶

Stampfer et al evaluated the efficacy of intravenous streptokinase in reducing mortality after acute myocardial infarction by pooling results of eight randomized clinical trials from 1969 to 1979.³⁷ Statistical analysis of results suggested that therapy with intravenous streptokinase after myocardial infarction reduced mortality by approximately 20% over the subsequent few weeks, with a protective effect suggested beyond the sixth week.

Spann et al reviewed the literature on the use of intravenous streptokinase in myocardial infarction and reported their experience with high-dose intravenous therapy in 13 patients under the age of 70 years with transmural myocardial infarction and duration of symptoms of less than six hours.³⁸ Streptokinase 850,000 IU IV was administered over one hour. Clot lysis and angiographically demonstrated coronary reperfusion were reported in six of these patients within one hour of starting the infusion in this ongoing study. Their review of the literature had indicated that successful recanalization after intravenous therapy has been reported in 45-65% of patients, as compared with 75% who received intracoronary infusion.

Encouraged by findings that thrombus formation is a frequent cause of total coronary occlusion in the early hours of myocardial infarction, several investigators have used streptokinase for intracoronary thrombolysis. Jerome Weinstein analyzed efficacy and safety data from 209 U.S. cases in the Hoechst-Roussel intracoronary streptokinase registry.³⁹ Successful recanalization was achieved in 76% of infarct-related occluded coronary arteries. Among the 209 cases, 14 adverse reactions associated with the use of streptokinase were reported. There were six cases of excessive bleeding or hematoma reported at the site of the insertion. Since all patients with bleeding problems were already heparinized, however, it is unclear to what extent streptokinase contributed to this complication.

In a study by Reduto et al, coronary angiography was performed on hospital admission in 32 consecutive patients with acute myocardial infarction.⁴⁰ Twenty-six patients had total occlusion of an infarct-related coronary artery. In 18 of these patients, intracoronary infusion of streptokinase resulted in reperfusion of the distal coronary artery. Hemodynamic indexes of left ventricular performance and ejection fraction did not change immediately after reperfu-

sion. The mean left ventricular ejection fraction increased significantly ($P=0.007$) from hospital admission to discharge in patients exhibiting reperfusion of the occluded coronary artery.

Markis et al evaluated intracoronary streptokinase 2.3-4.3 hours after the onset of symptoms in nine patients with acute myocardial infarction.⁴¹ Occluded coronary arteries were opened in all patients, but reocclusion occurred in one patient. Improved regional perfusion was observed in seven of nine patients.

Despite limited data, thrombolysis with streptokinase, either by intracoronary or intravenous administration, appears promising in the treatment of acute myocardial infarction. Although coronary thrombolysis appears to occur more frequently with the intracoronary route of administration, the intravenous route will enable treatment of a larger number of patients. In addition, streptokinase can be administered earlier by the intravenous rather than the intracoronary route due to its simplicity. This is important, since coronary thrombolysis can be achieved much more quickly and effectively when the drug is administered early.³⁴⁻⁴¹ The sooner reperfusion of the coronary artery is achieved with streptokinase, the greater the chances of salvaging the jeopardized myocardium.

Arteriovenous Cannula Occlusion

Streptokinase has been used for clearing of totally or partially occluded arteriovenous cannulae.¹⁵ Retrombosis of these shunts, however, may occur at a variable interval.¹¹

Miscellaneous Uses

Thrombolytic agents have also been investigated in numerous other clinical situations. Streptokinase has been used in obstruction of the bronchus by clots, retinal vein thrombosis, heart valve obstruction, obstruction of the peritoneal dialysis catheter, and hemothorax.⁴²⁻⁴⁶ Urokinase has been used in cerebral infarction and renal-cortical necrosis.^{47, 48}

Dosage and Administration

Streptokinase is available as Streptase from Hoechst-Roussel Pharmaceuticals and as Kabikinase from Kabi Group. Streptase is supplied as a lyophilized white powder in vials containing 250,000 and 750,000 IU of purified streptokinase. Kabikinase is available in 5 ml vials containing 250,000, 600,000 and 750,000 IU per vial of purified streptokinase. A loading dose of streptokinase is required to neutralize streptococcal antibodies present in the circulation. In the United States, a loading dose of 250,000 IU, administered intravenously over 30 minutes, has been found to be appropriate in approximately 90% of patients.¹⁵ A maintenance dose of 100,000 IU/hour for 12-72 hours follows the loading dose. Although the optimal duration of therapy has not yet been established, streptokinase is usually given for 24 hours to patients with pulmonary embolism, and for 72 hours for deep vein thrombosis.¹⁵ When administered via the intracoronary route, a bolus dose averaging 20,000 IU and a maintenance dose averaging 2,000 IU/min for 60 minutes has resulted in opening of occlusions within one hour in greater than 75% of patients. The duration of

therapy for acute myocardial infarction varies from 12-72 hours in most studies.³⁴⁻⁴¹ In most patients the thrombin time will be prolonged two to five times the normal control value. If the thrombin time after four hours of therapy is less than 1½ times the normal control value, therapy should be discontinued because of the possibility of excessive resistance due to high streptococcal antibody titers from a recent streptococcal infection.^{11, 15-17}

Urokinase is available as Abbokinase from Abbott Laboratories and Breokinase from Breon Labs. Both are supplied as a sterile lyophilized preparation. Each vial contains 250,000 IU urokinase activity. A priming dose of urokinase 4400 IU/kg, dissolved in normal saline, is administered over a period of 10 minutes. This is followed by a continuous infusion of 4400 IU/kg/hour for 12 hours. The total volume of fluid administered should not exceed 200 ml.¹⁴

Following thrombolytic therapy with either drug, treatment with heparin by continuous infusion without an initial bolus is recommended. Heparin treatment should not begin, however, until the thrombin time has decreased to less than twice the normal value.

Adverse Effects

Bleeding. The incidence of major bleeding has been reported to be about 5-20% with streptokinase and urokinase.^{17, 22, 27} Minor bleeding secondary to venous cutdowns and other causes has been reported to be about 20% with thrombolytic agents.^{14, 15}

In cases of serious bleeding, streptokinase therapy must be discontinued and plasma administered. If very rapid reversal of the fibrinolytic state is required, treatment with aminocaproic acid can be instituted.^{11, 15} Aminocaproic acid inhibits activation of plasminogen by streptokinase and is usually given in a dose of 5 g during the first hour, followed by a continuous infusion of 1 g/hour until the hemorrhagic condition is under control.¹¹

Hypersensitivity Reactions. Hypersensitivity reactions associated with streptokinase include urticaria, itching, flushing, nausea, headache (12%), transient elevation or decrease of systolic blood pressure of greater than 25 mm Hg (2%), and anaphylaxis (1.3-2.5%).^{15, 17, 28}

Although urokinase is a protein of human origin, *in vitro* and *in vivo* tests have shown no evidence of inducing antibody formation. The possibility of serious allergic reactions cannot be excluded.

Fever. With streptokinase use, the incidence of temperature elevation greater than 1.5°F is 30%, but only 3.5% have temperatures in excess of 104°F.^{17, 22, 27, 30} Febrile episodes with urokinase have occurred in approximately 15% of patients.¹⁷

Phlebitis. The incidence of phlebitis at the infusion site is about 2%, and further dilution of streptokinase helps alleviate this problem.¹⁵

Summary and Conclusion

All the studies reviewed agree that thrombolytic agents are superior to heparin alone in accelerating the lysis of pulmonary thromboemboli, restoring normal pulmonary circulation, and decreasing elevated right heart pressures. No significant differences, however, in overall morbidity and mortality have been noted between most heparin-treated and streptokinase-treated patients. In patients with massive pulmonary embolism and shock, several studies have shown a significantly higher recovery rate with thrombolytic agents if used within the first 72 hours after onset of symptoms.¹⁶⁻²²

Streptokinase was also found to be more effective than heparin in the lysis of extensive ileo-femoral thrombi if used within seven days from the onset of symptoms.²³

The use of streptokinase in the treatment of acute myocardial infarction appears promising, with coronary thrombolysis occurring more frequently when the drug is administered via the intracoronary route. Further studies are necessary to determine whether long-term morbidity and mortality are decreased.

In conclusion, the use of streptokinase should be limited to patients with massive pulmonary embolism with shock, proximal deep vein thrombosis, and arteriovenous cannula occlusion. The use of regional streptokinase in acute myocardial infarction seems promising, although this therapy should be reserved for those patients refractory to the more conventional types of treatment. Although the approved indications for urokinase are limited to pulmonary embolism and arteriovenous cannula occlusion, the therapeutic and toxic differences between it and streptokinase appear to be insignificant. Since urokinase is much more expensive, streptokinase should be considered the thrombolytic agent of choice.

NOTE: Complete bibliography is available through the office of the North Carolina Medical Journal, Box 3910 Duke Hospital, Durham 27710.

Price per vial

Streptokinase		
<i>Kabikinase</i>		<i>Streptase</i>
250,000 IU —	\$33.75	250,000 IU — \$42.24
600,000 IU —	\$63.75	750,000 IU — \$93.24
Urokinase		
<i>Abbokinase</i>		
250,000 IU —	\$154.38	

Premarital Legal Requirements

Louise H. Poe, MT (ASCP), MPH

THIS article is designed to eliminate some of the confusion that surrounds the physical examination and laboratory tests required for a marriage license. Requirements vary among states and are subject to frequent changes. The following general information concerns both in-state and out-of-state premarital requirements.

North Carolina Requirements

North Carolina *does not* have a statute that requires a premarital laboratory test of any kind. North Carolina does have a requirement (G.S. 51-9) that a health certificate be presented to the Registrar of Deeds when securing a marriage license. This certificate (Division of Health Services [DHS] No. 1836) must be signed and dated by a licensed physician. It is left to the discretion of the examining physician to decide by the "usual means of examination" if the applicant meets the "requirements" set forth in G.S. 51-9. These requirements are found on the back of DHS 1836.

Out-of-State Requirements

Persons planning to be married in another state must satisfy the requirements of the state in which the marriage is to be performed. These requirements may include performance of laboratory tests in approved laboratories. Most states will accept laboratory test results in the following facilities:

- State health laboratories
- Hospitals accredited by the Joint Commission on Accreditation of Hospitals
- Hospitals otherwise approved to participate in the Medicare program
- Federal laboratories (Veterans Administration, Public Health Service Hospitals and military hospitals and/or institutions)
- Independent laboratories that participate in the Medicare and/or Clinical Laboratory Improvement Act program.

A few states will not accept any laboratory test results from an out-of-state laboratory. A few states have no requirements for premarital laboratory tests or examinations.

Other Approved Laboratories

Although the North Carolina law requiring premarital syphilis serology testing has been repealed, there is a law that requires a test for prenatal syphilis serology. The Department of Human Resources, Division of Facility Ser-

vices approves laboratories for this purpose. They may be found in hospitals, health departments or other facilities such as clinics and physicians' offices. If other states require a premarital syphilis test, they will usually accept test results from laboratories that are approved by the Department of Human Resources for prenatal syphilis serology to satisfy this requirement.

Branch Laboratories

Some states have branches of their state health laboratories; test results are usually accepted from these branches for marriage licenses. Even though the North Carolina Division of Health Services Laboratory Section does not have branches, county health department laboratories come under the state's certification program (for prenatal syphilis serology only) and would, therefore, be acceptable to most other states for premarital syphilis serology testing.

Authorized Persons

Out-of-state premarital application forms may have a laboratory result section requiring the signature of an "authorized person" (i.e., an official of the North Carolina Department of Human Resources). Should this be the case, the form may be mailed to the Chief, Licensure and Certification Section, Division of Facility Services, Department of Human Resources, P.O. Box 12200, Raleigh 27605-2200. This individual has the authority to certify that a laboratory is approved (licensed and/or certified). After signing, the Chief of the Licensure and Certification Section will return the form to the physician or laboratory. If the test is performed in the North Carolina Division of Health Services Laboratory the technologist who performed the test may sign the form.

Requirements for Licensed Physicians

The requirement that a licensed physician perform the premarital examination varies among states. Some states require that the physician be licensed in the state where the marriage is to be performed. Other states will accept a physical examination performed by a physician licensed in another state. North Carolina will accept documentation from any licensed physician in any state or territory of the United States, the District of Columbia or Puerto Rico. Most states will accept the premarital examination from a medical officer of the armed forces or Public Health Service, even though he may be licensed in another state and is temporarily on a tour of duty.

Acceptable Premarital Forms

Some states will not accept any form or premarital ex-

From the Licensure Unit, Division of Facility Services, Department of Human Resources, Raleigh 27605.

inations except their own. It is advisable to obtain information about requirements and required forms from the State Health Department or local Registrar of Deeds where the marriage will occur. Out-of-state forms may be obtained for most states from the North Carolina Division of Health Services Laboratory. North Carolina will accept an out-of-state form if the other state has a comparable law.

Marriage License Requirements

North Carolina does require a marriage license. General Statute 51-6 states that marriage without a license is unlawful and that no minister or officer shall perform a ceremony of marriage until a marriage license is delivered to him signed by the Registrar of Deeds in the county in which the marriage is intended to take place.

Age Limits and Other Requirements

Each state has different requirements for obtaining a marriage license. These may include age limits ranging from 13 to 21, with different ages applying to men and women. In some states a woman may obtain a marriage consent if she is pregnant although she may be under age. In other states consent may require a court order, consent of one or both parents, consent of a probate judge or combination of a host of other requirements. In North Carolina the legal minimum age for marriage is 18 for both men and

women and consent is required if the marriage applicants are younger.

Summary

Agencies in North Carolina that will assist the physician and marriage applicants in meeting the premarital syphilis serology testing requirements of another state are:

For out-of-state forms

North Carolina State Laboratory of Public Health
Virology/Serology Branch
P.O. Box 28047
Raleigh, NC 27611
Telephone: 919/733-7544

Health Certificate (DHS-1836)

Division of Health Services
Mailing Unit
P.O. Box 2091
Raleigh, NC 27602
Telephone: 919/733-7206

Laboratory Certification Program

Division of Facility Services
Licensure and Certification Section
Licensure Unit
P.O. Box 12200
Raleigh, NC 27605
Telephone: 919/733-2786

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An Update on Physician Assistants: The N.C.A.P.A. Survey

Wayne W. VonSeggen, PA-C and John F. Bolles, PA-C

DURING 1982 the North Carolina Academy of Physician Assistants, with the encouragement of the Committee on Allied Health Professionals of the North Carolina Medical Society, prepared an 80-question survey and sent it to the 406 physician assistants (PAs) registered to practice in North Carolina. The return rate was 60% (244/406). The purpose of this 1982 survey was to gather information to assess the following general areas:

What are the current demographic statistics on physician assistants in North Carolina?

What are characteristics of the medical practices where physician assistants are employed?

What are the current salaries, compensations and benefits among North Carolina physician assistants?

How are physician assistants being supervised by their employing physicians?

What do physician assistants feel about several issues that are facing them?

General Demographic Information

The average age of all North Carolina PAs is 33.4. The average male age is 34 years, and 70% are male. The average female age is 32 years. The fact that 30% of practicing PAs are female indicates a significant change in the pool of individuals entering this profession. Early studies showed nearly complete male preponderance since the individuals initially being trained as PAs had military medical corpsman experience. In recent years, some PA programs in N.C. have been training classes composed of up to 50% females.

Ninety-one percent of practicing PAs are Caucasian and 6.6% are Afro-American; 0.4% are "other" races, and 2.0% chose not to answer.

The average number of years of health care experience prior to entering the PA profession is 4.7 years. Some PAs have had up to 10 years prior health care experience.

Eighty-nine percent are graduates of a 24-month PA training program. Six percent have had formal PA training longer than 2 years. Only 4% have had training of between 1 and 2 years. No PA in N.C. has had less than 1 year of formal training.

Ninety-one percent of PAs in North Carolina have passed the certifying exam by the National Commission on Certification of Physician Assistants (NCCPA). Since at

the time of survey the N.C. Board of Medical Examiners required all new PAs to pass this exam before being registered, the other 9% probably represent the number of PAs who were "grandfathered" under provisions of the NCAC 32D.0003(3): "Applicants who have graduated prior to December 31, 1980 shall be exempt from NCCPA certification."

Membership in physician assistant organizations has increased in recent years. Now 53.4% of North Carolina PAs responding to this survey are members of the American Academy of Physician Assistants. Approximately 50% of all PAs in the United States are members of the AAPA to date.

The average length of time in practice in this survey is about 5 years; the range is 6 months to 11½ years. Forty-five percent (111) have had only one job since becoming a PA; 35% (86) have had two different (successive) employers as a PA; 19% have had three or more jobs since beginning PA practice.

Practice Information

The PAs were asked to indicate the general type of practice in which they are employed:

- 24% (59) — Family Practice
- 14% (34) — Internal Medicine
- 10.7% (26) — Emergency Medicine
- 18.5% (45) — Surgery
- 32.5% (79) — Other

Over 60% of these "other" practices included Psychiatry, Pediatrics, Health Clinics, Occupational Medicine, OB-Gyn, Alcohol Treatment-Detoxification Clinics, and Rehabilitation Medicine.

The PAs described their present practice employer as follows:

- 22% (54) work with a solo M.D.
- 6.8% (16) work with a two-M.D. partnership.
- 24% (57) work with a group practice.
- 27.4% (65) are employed by M.D.'s at a hospital.
- 19% (45) are employed in other situations, such as an HMO, a corporation, university, or other organization.

The PAs were asked to give the number of physicians who have a part in their supervision. The results are:

- 32.2% (77) have one supervising physician.
- 24.6% (59) have two supervising physicians.
- 11.7% (28) have three supervising physicians.

This survey was supported by North Carolina Academy of Physician Assistants.

- 9.2% (22) have four supervising physicians.
- 17.1% (41) have five to nine supervising physicians.
- 5% (12) have 10 or more supervising physicians.

(Note: All PAs have one primary supervising physician regardless of the number of backup supervising physicians.)

The PAs were requested to give the number of other PAs in their practice:

- 58% (138) are the only PA in their practice.
- 19% (45) work with one other PA.
- 23% (56) work with more than one other PA in their practice.

Twenty-six percent of the PAs describe their practice setting as being located in a medically underserved area.

By population of their practice area, 28% say they are employed in an area of less than 15,000. Another 24% work in an area with a population of between 15,000 and 50,000.

There is wide variation in the scheduled hours to work and wide variations in on-call responsibilities among PAs. The average scheduled working hours for a PA are probably 45-50 hours per week.

Office vs. Hospital Practice

The PAs were questioned about the percentage of their time they spend working in an office/clinic setting or in a hospital setting. Their responses follow:

Percent of working time	Office/clinic setting	Hospital setting
0	28.5%	27 %
25	55	21.7
33	4.6	5.3
50	9.4	8.2
66	6.8	3.7
75	17.8	4.1
100	27.2	30

Hospital Privileges

In this study, 13.3% of the PAs say that hospital privileges are *not* required in their present work setting; 190 (79%) have hospital privileges. In a related question, 178 PAs in this survey said that they worked some part of their day in a hospital. It is possible that some PAs may have been in the process of gaining hospital privileges since 8 of 18 PAs without hospital privileges have been in practice less than 2 full years. For those (5) who do not have hospital privileges and who have been in PA practice over 5 years, only one has had two different employing practices. The other 4 PAs are still in their initial employing practice, indicating either satisfaction with the arrangement or resignation to the situation.

Job Description

62% consider their position "mostly primary care." When asked to describe the major responsibilities of their job, these were their responses:

- Clinical 96.3% (235)
- Administration 2.5% (6)

- Teaching 0.8% (2)
- Research 0.5% (1)

The source of funding for the present job of the PAs was given as:

- Private 52.0% (123)
- State 19.5% (46)
- Federal 7.6% (18)
- Corporation 16.5% (39)
- Other 3.8% (9)

Only 21% of the PAs have actually signed a written contract, but 80% would recommend a written contract for a PA.

The types of practice PAs are now working in are:

- Family Practice/Family Medicine 24.3% (59)
- Internal Medicine 14.0% (34)
 - (includes Cardiology, Gastroenterology, Hematology, Oncology, Nephrology, Pulmonary, Allergy, Critical Care, Rheumatology)
- Emergency Medicine 10.7% (26)
- Surgery 18.5% (45)
 - (includes Orthopedics, Plastics (Burn Center), General, ENT, Neurosurgery, Ortho-Hand, Urologic, Vascular)
- Other 32.5% (79)
 - (includes Psychiatry, Pediatrics, Health Clinic, Occupational Medicine, OB-Gyn, Alcohol Treatment-Detoxification Clinic, Rehabilitation, 4 each; Cardiology, Computer Research, Dermatology, Family Practice and E.R., Geriatrics, Hematology, Hospital Admissions, Institutional, Neurology, Ophthalmology, Planned Parenthood, Rural Health Clinic, University Student Health Clinic, Urology, VA (unspecified), Correctional, Pediatric Hematology-Oncology)

Compensation and Benefits of PAs

The average base salary per year (not including fringe benefits) for all PAs answering this part of the survey (N = 234) was \$22,436. The average for male PAs was \$23,311, for female PAs \$20,491.

The gender averages may not be as dependent upon gender as they are upon the fact that in the earlier years of PA training the pool of applicants for PA programs was ex-military corpsmen. These males would tend to have higher salaries now simply because they have been in practice longer.

Table 1 lists the salaries and length of time as a PA. Table 2 lists salaries and years in present position as a PA. Table 3 lists salary averages in different types of practice.

The average percent increase in the base salary per year since accepting their present job was 10.7%. The average number of sick days allotted per year was 10.7 days; about 9% have no specified maximum number but use what they need. The average number of vacation days allotted per year is 14, with a range of zero to 36 days.

The following benefits table was presented to the PAs in the survey. The number at the left represents the percentage of PAs in this survey who receive that benefit.

- 54% Life insurance at no charge
- 27% Life insurance at a group rate

Table 1
Salary vs. Years as P.A.

Years as P.A.	Average Salary	Range	
Less than one year (N = 3)	\$16,167	\$16,000	\$16,500
One year (N = 6)	18,091	16,200	19,600
Two years (N = 32)	19,833	15,000	28,000
Three years (N = 35)	21,002	16,000	27,500
Four years (N = 42)	23,298	16,000	33,960
Five years (N = 28)	22,805	17,000	28,000
Six years (N = 22)	26,057	18,000	38,000
Seven years (N = 9)	26,167	21,000	34,000
Eight years (N = 19)	25,899	16,000	31,200
Nine years (N = 16)	28,268	19,200	40,000
Ten years (N = 14)	25,771	18,000	32,000
Over ten years (N = 6)	24,983	18,000	29,700

Table 2
Salary vs. Years in Present Position as P.A.

Years in Present Position	Average Salary	Range	
Less than one year (N = 11)	\$18,163	\$16,000	\$22,400
One year (N = 39)	20,713	16,200	40,000
Two years (N = 51)	20,363	15,000	28,000
Three years (N = 34)	22,627	16,000	35,000
Four years (N = 25)	22,218	18,000	33,960
Five years (N = 20)	24,874	16,000	31,290
Six years (N = 16)	25,116	19,000	38,000
Seven years (N = 16)	25,584	20,000	31,200
Eight years (N = 4)	27,500	24,000	32,000
Nine years (N = 7)	24,586	18,000	30,000
Ten years (N = 5)	24,040	22,000	26,700
Over ten years (N = 2)	21,750	18,000	25,500

Table 3
Salary Averages for Different Types of Practices

Type of Practice	Number of Respondents	Average Salary
Family Practice	59	\$22,457.27
Internal Medicine	34	\$22,758.73
Emergency Medicine	26	\$23,076.00
Surgery	45	\$23,195.61
Other	79	\$21,617.71

- 53% Personal health insurance at no charge
- 25% Personal health insurance at reduced charge
- 16% Family health insurance at no charge
- 39% Family health insurance at reduced charge
- 50% Disability insurance paid by employer
- 22% Profit sharing
- 78% Allotment for continuing medical education paid by employer. (Average of \$641/year for those who filled in a designated amount for CME.)
- 43% Professional organization fees paid by employer
- 46% Recertification fees (NCCPA) paid by employer
- 86% Malpractice coverage provided at employer's expense
- 53% Pension plan or IRA or long-term investments provided
- 90% time off to attend CME events
- 81% Do not have to use vacation time when attending CME events, paid as if they were working in their own practice

Supervision of Physician Assistants

PAs are trained to work as dependent physician extenders providing health care services under the supervision of a physician. Each registered PA in North Carolina must by definition have a primary supervising physician, registered with the N.C. Board of Medical Examiners (NCBME), who is ultimately responsible for the actions and services provided by the PA under that physician's supervision. Many PAs work in group practices, where they have a single supervising physician and one or more backup supervising physicians.

The average number of supervising physicians for the PAs in this survey is 3.4 physicians per PA. Here is a further analysis:

- 31.5% (76/241) have a single supervising physician
- 24.0% (58/241) have two supervising physicians (one primary and one backup)
- 11.6% (28/241) have three supervising physicians
- 9.1% (22/241) have four supervising physicians
- 22.0% (53/241) have five or more supervising physicians

A majority (55.5%) of PAs in North Carolina are supervised by solo or two-physician practices. Only 11 PAs (4.5%) listed 10 or more physicians who have a part in their supervision. Many PAs have one or two physicians with whom they interact daily and are supervised by, but may in fact have several backup physicians to be available when the primary physician is unavailable, such as during illness, medical meetings, days off, or vacations.

Of the PAs surveyed, 94.4% are satisfied with the degree of supervision by their physicians; 92% feel that the relationship with their supervising physician is "satisfactory."

There are a variety of methods of supervising a PA including actual physical presence of the physician, chart review by the physician, telephone consultations, and time-saving written standing orders for the PAs. Standing orders are standardized treatment protocols for typical problems encountered in their practice.

Sixty percent of PAs have their supervising physician physically on site all the time. Another 18% say their supervising physician is on site where they are working 50% of the time. Another 12% say their supervising physician is on site less than 50%, while only 3% say their supervising physician is on site one day per week. (Note: For those times when the physician is not on site, other methods are available for the PA to consult the physician, or chart review is being done.)

Daily chart review of the PA is a method of supervision used by 54% of supervising physicians, in addition to other methods. Weekly chart review is used by 10%. Sporadic chart review is used by 10% of the supervising physicians. Phone consultation in some manner between the PA and the physician is used by 33% of the practices. Of those who have weekly chart review or sporadic chart review, 84% have their supervising physician on site all the time. There were no PAs in this survey who gave "sporadic chart review" or "phone consultation" as their only method of supervision.

The only type of supervision that concerned the authors was "M.D. on site one day per week" plus "weekly chart review by M.D." This combination of supervision seems to be less than the recommendations set by the NCBME. The other 99.5% of PAs listed various combinations of physician supervision that would seem to insure adequate PA supervision by a physician.

Many practices make use of written standing orders. About 10% of the practices do not use written standing orders because the physician is on site 100% of the time. About 80% of the practices in this survey either have standing orders or are currently developing standing orders. Another 9.4% do not use standing orders as part of their methods of PA supervision.

For those who have written standing orders, 24% are using "Patient Care Guidelines for FNPs" by Hoole, Pickard, and Greenburg; 36% developed their own set of standing orders; 34.7% are using a combination of the two; and 4.7% are using other prepared standing orders such as the "Washington Manual," or other printed clinical protocols.

Issues Facing Physician Assistants in North Carolina

At the time this survey was taken in 1982, the NCBME required each PA in the state to have passed the national certification examination for primary care physician assistants by the NCCPA (National Commission on Certification of Physician Assistants). Several of the questions on the survey dealt with PAs' attitudes about NCCPA certification.

On the survey, 38.6% felt that passing the NCCPA exam should be a mandatory requirement for PA registration. (Note: On July 1, 1983 the NCBME dropped NCCPA

certification as a requirement for PA registration despite much testimony supporting the retention of the NCCPA exam as a part of registration in North Carolina.)

The PAs are fairly evenly divided in their view of the current Formulary for Physician Assistants, with 50.7% satisfied with the Formulary and 49.3% dissatisfied with it. For those who indicate dissatisfaction, the following general categories of suggestions for improvement were offered:

1. Clarify limitations on outpatient prescriptions vs. inpatient medication order writing.
2. It should be OK for PAs to write prescriptions for OTC medications.
3. Improve refill policy, especially for those patients not needing monthly reassessment.
4. Include approval for up to 3-month amounts of all antihypertensive medications and insulin.
5. Include approval for codeine in some limited form, either on a 24- or 48-hour limited prescription amount as an analgesic, or as part of Schedule IV or V (antidiarrheals and antitussives) in limited amounts.
6. Include tetracyclines, topical cleocin for acne, and chloromycetin ophthalmic preparations on a limited basis.
7. Expand refill authority for oral contraceptives.
8. Clarify the fact that additional authority to prescribe may be granted for specific situations upon request and subsequent approval by the NCBME.

On the survey, PAs were asked to rate the present employment opportunities for PAs in their area of North Carolina compared with three years ago. The results were:

- 9.4% — much better now than three years ago
- 21.4% — slightly better now than three years ago
- 33.5% — about the same as three years ago
- 23.7% — slightly worse than three years ago
- 12.1% — much worse now than three years ago

On another question regarding employment, the PAs were asked: "Have you been impeded from accepting or being considered for a specific job opportunity because of the BME's current policy of not registering PAs before NCCPA scores are received?" Of those to whom this policy applies, 9.2% (6/59) said they have been impeded by that policy. (Note: Since the NCBME has dropped NCCPA certification as a requirement for PA registration, there is no longer any "exam score delay" among recent graduates as far as registration is concerned.)

Of the PAs in this survey, 25% said that the lack of Medicare reimbursement for the services of PAs has been a problem in their personal practice.

The most definitive answer in the survey, about which the largest number of PAs agreed, came when they were asked whether they thought that the NCBME should have an advisory committee on PAs. A resounding 98.3% answered that the NCBME should have a formal advisory committee on PA matters. When given the opportunity to select their choice for the composition of such a committee, 70% chose a combination of PAs, supervising physicians, and representatives from PA training programs in North Carolina; 26% chose a combination of PAs and supervising physicians for such a committee; only 1% chose an option

that would have an advisory committee composed of physicians without PA representation.

Physician assistants are required to maintain 100 hours of continuing medical education every two years to retain membership in the national organization, the American Academy of Physician Assistants. The most popular ways to fulfill CME requirements are (in order of popularity):

- 76% CME sponsored by a local group
- 54% PA program-sponsored CME
- 47% Book and journal reading
- 44% NCAPA Conference
- 41% CME outside of North Carolina
- 36% Teaching
- 29% AAPA Conference
- 29% PA Journal (mailable CME exams)
- 15% Chart review
- 4% Research

At this time the number of PAs using CME sponsored by the N.C. Medical Society is negligible, even though PAs have been informally invited to participate. Of the PAs in this survey, 78% responded that their primary supervising physician is a member of the N.C. Medical Society. The PAs were asked: "If the opportunity presented itself, would you like to be an associate member of the N.C. Medical Society?" and a surprising 81% said "yes." It is possible that additional efforts by the N.C. Medical Society to include PAs in their CME activities could result in strong support among PAs seeking to acquire quality in-state CME.

The PAs were asked how they like being a PA. Ten percent chose "exceeds my expectations"; 17.5% chose "falls short of my expectations"; 66% chose "meets my expectations"; 6.1% chose "dissatisfied." No attempt was made to correlate dissatisfaction with those who said they are dissatisfied with their supervising physician or the quality of their supervision. However, 5.3% said they are not satisfied with the degree of supervision they have. No followup question was asked to determine whether the dissatisfaction might be caused by too little supervision, restrictive supervision, personality conflict, interprofessional problems, or purely deficient benefits.

We were interested in learning whether these PAs had at some time in their careers encountered active opposition to the PA profession. About 20% said they have experienced some opposition at some time. The most common source of opposition to the PA profession is from occasional nursing personnel and occasional hospital staff members. Despite occasional opposition, approximately half (48.9%) of the PAs said they would like to work a second job as a PA. In a followup question, 43.5% said they need another source of income to supplement their earnings from their current PA practice to meet their needs.

The job satisfaction among the PAs in this survey is evidently quite high, since 92.5% of the PAs indicated they intend to continue working as a PA for the next four years.

Summary

The physician assistant profession had its origins in North Carolina. The first PA training program started at Duke University in 1965. The American Academy of Physician Assistants was initially organized by North Carolina PAs. In this report, the current status of the PA profession in North Carolina has been described from information given in answers by PAs to an 80-question survey by the North Carolina Academy of Physician Assistants.

We hope this report will give North Carolina physicians an improved understanding of the physician assistant profession. For those physicians who currently do not employ a physician assistant in their practice, this report provides an overview of current salary, benefits, supervision methods, and attitudes of 60% of the PAs working in this state. Such information could be helpful to physicians seeking to remain competitive in the current medical marketplace where many efficient, active practices are utilizing PA services. For those physicians already supervising physician assistants, we hope this report will provide the basis for additional MD-PA interactions regarding improving supervision and upgrading benefits of the physician assistants on your health care team.

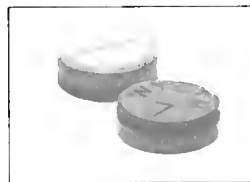
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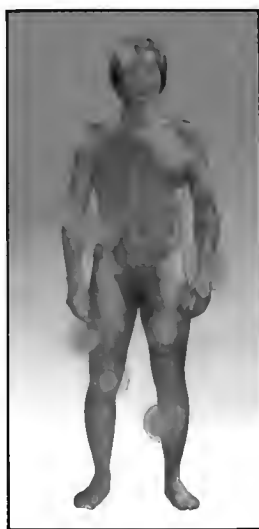
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when anxiety magnifies the perception of pain

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3 or 4 times daily

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(BRIEF SUMMARY)

DESCRIPTION

Each tablet contains 200 mg meprobamate and 325 mg aspirin.

INDICATIONS

Adjunct in short-term treatment of pain accompanied by tension and/or anxiety in patients with musculoskeletal disease. Clinical trials demonstrated that in these situations relief of pain is somewhat greater than with aspirin alone. Effectiveness in long term use, i.e., over 4 months, has not been assessed by systematic clinical studies. Physicians should periodically reassess usefulness of drug for individual patients.

CONTRAINDICATIONS

ASPIRIN: Allergic or idiosyncratic reactions to aspirin or related compounds.

MEPROBAMATE: Acute intermittent porphyria; allergic or idiosyncratic reactions to meprobamate or related compounds; e.g. (carbamazepine, meprobamate, or carbamazepine).

WARNINGS

ASPIRIN: Use salicylates with extreme caution in patients with peptic ulcer, asthma, coagulation abnormalities, hypoprothrombinemia, vitamin K deficiency, or those on anticoagulants. In rare instances, aspirin in persons allergic to salicylates may result in life-threatening allergic episodes.

MEPROBAMATE: DRUG DEPENDENCE

Physical and psychological dependence, and abuse have occurred. (Gross) intoxication from prolonged ingestion of usually greater than recommended doses is manifested by ataxia, slurred speech, and vertigo. Therefore, carefully supervise dose and amounts prescribed and avoid prolonged use, especially in alcoholics and others with known propensity for taking excessive quantities of drugs. Sudden withdrawal after prolonged and excessive use may precipitate recurrence of preexisting symptoms.

toms, e.g. anxiety, anorexia, or insomnia, or withdrawal reactions, e.g. vomiting, ataxia, tremors, muscle twitching, confusional states, hallucinations, and rarely convulsive seizures.

Such seizures are more likely in persons with CNS damage or preexisting or latent convulsive disorders. Onset of withdrawal symptoms occurs usually within 12 to 48 hours after discontinuation; symptoms usually cease within next 12 to 48-hour period. When excessive dosage has continued for weeks or months, reduce dosage gradually over 1 to 2 weeks rather than stop abruptly. Alternatively, a short-acting barbiturate may be substituted, then gradually withdrawn.

POTENTIALLY HAZARDOUS TASKS: Warn patients meprobamate may impair mental or physical abilities required for potentially hazardous tasks; e.g. driving or operating machinery.

ADDITIONAL EFFECTS: Since CNS-suppressant effects of meprobamate and alcohol or meprobamate and other psychotropic drugs may be additive, exercise caution with patients taking more than one of these agents simultaneously. **USE IN PREGNANCY AND LACTATION:** An increased risk of congenital malformations associated with minor tranquilizers (meprobamate, chloralhydrate, and diazepam) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. The possibility that a woman of child-bearing potential may be pregnant at time of institution of therapy should be considered. Advise patients if they become pregnant during therapy or intend to become pregnant to communicate with their physicians about desirability of discontinuing the drug.

Meprobamate passes the placental barrier. It is present both in umbilical-cord blood at or near maternal plasma levels and in breast milk of lactating mothers at concentrations two to four times that of maternal plasma. When use of meprobamate is contemplated in breastfeeding patients, consider the drug a higher concentration in

breast milk as compared to maternal plasma levels.

USAGE IN CHILDREN: Keep preparations with aspirin out of reach of children. Equagesic[®] (meprobamate with aspirin) is not recommended for patients 12 years of age and under.

PRECAUTIONS

ASPIRIN: Salicylates antagonize uncoupling activity of probenecid and sulfinpyrazone. Salicylates are reported to enhance hypoglycemic effect of sulfonylurea anti-diabetics.

MEPROBAMATE: Use lowest effective dose, particularly in elderly and/or debilitated, to preclude over-sedation. Meprobamate is metabolized in the liver and excreted by the kidney; to avoid excess accumulation exercise caution in its use in patients with compromised liver or kidney function. Meprobamate occasionally may precipitate seizures in epileptic patients. It should be prescribed cautiously and in small quantities to patients with suicidal tendencies.

ADVERSE REACTIONS

ASPIRIN: May cause epigastric discomfort, nausea, and vomiting. Hypersensitivity reactions, including urticaria, angioneurotic edema, purpura, asthma, and anaphylaxis may rarely occur. Patients receiving larger doses of salicylates may develop tinnitus.

MEPROBAMATE: CNS Drowsiness, ataxia, dizziness, slurred speech, headache, vertigo, weakness, paresthesias, impairment of visual accommodation, euphoria, overstimulation, paradoxical excitement, fast EEG activity. GI: Nausea, vomiting, diarrhea.

CARDIOVASCULAR: Palpitation, tachycardia, various forms of arrhythmia, transient ECG changes, syncope, hypotensive crisis.

ALLERGIC OR IDIOSYNCRATIC: Milder reactions are characterized by itchy, urticarial, or erythematous maculopapular rash, generalized or confined to the groin. Other reactions include exanthema, acute hemorrhagic purpura, petechiae, ecchymoses, eosinophilia, peripheral edema, adenopathy, fever, fixed drug eruption with cross-reaction to carbamazepine and cross-sensitivity between meprobamate, meprobamate and meprobamate, carbamazepine. Rare: more severe hypersensitivity

reactions include hyperpyrexia, chills, angioneurotic edema, bronchospasm, oliguria, and anuria. Also anaphylaxis, exfoliative dermatitis, stomatitis, and proctitis. Stevens-Johnson syndrome and bullous dermatitis have occurred.

HEMATOLOGIC (SEE ALSO "ALLERGIC OR IDIOSYNCRATIC") Agranulocytosis, aplastic anemia have been reported, although no causal relationship has been established, and thrombocytopenic purpura.

OTHER: Exacerbation of porphyric symptoms.

DOSEAGE AND ADMINISTRATION: Usual dose is one or two tablets, 3 to 4 times daily as needed for relief of pain when tension or anxiety is present. Not recommended for patients 12 years of age and under.

OVERDOSEAGE

Treatment is essentially symptomatic and supportive. Any drug remaining in the stomach should be removed. Induction of vomiting or gastric lavage may be indicated. Activated charcoal may reduce absorption of both aspirin and meprobamate. Aspirin overdose produces usual symptoms and signs of salicylate intoxication. Observation and treatment should include management of hyperthermia, specific parenteral electrolyte therapy for ketoadidosis and dehydration, watching for evidence of hemorrhagic manifestations due to hypoprothrombinemia which, if it occurs, usually requires whole blood transfusions. Suicidal attempts with meprobamate have resulted in drowsiness, lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse. Some suicidal attempts have been fatal. The following data, reported in the literature and from other sources, are not expected to correlate with each case (considering factors such as individual susceptibility and length of time from ingestion to treatment), but represent usual ranges reported. Acute simple overdose (meprobamate alone): Death has been reported with ingestion of as little as 12 grams meprobamate and survival with as much as 40 grams.

BLOOD LEVELS: 0.5-2.0 mg percent represents usual blood-level range of meprobamate after therapeutic doses. The level may occasionally be as high as 3.0 mg percent. 3-10 mg percent usually corresponds to findings of mild-to-moderate symptoms of overdose, such as stupor or light coma. 10-20 mg percent usually corresponds to deeper coma, requiring more intensive treatment. Some fatalities occur. At levels greater than 20 mg percent, more fatalities than survivals can be expected. Acute combined overdose (meprobamate with other psychotropic drugs or alcohol): Since effects can be additive, history of ingestion of a low dose of meprobamate plus any of these compounds (or of a relatively low blood or tissue level) cannot be used as a prognostic indicator.

In cases of excessive doses, sleep ensues rapidly and blood pressure, pulse, and respiratory rates are reduced to basal levels. Any drug remaining in stomach should be removed and symptomatic treatment given. Should respiration or blood pressure become compromised, respiratory assistance, CNS stimulants, and pressor agents should be administered cautiously as indicated. Diuresis, osmotic (mannitol) diuresis, peritoneal dialysis, and hemodialysis have been used successfully in removing both aspirin and meprobamate.

Anakization of the urine increases excretion of salicylates. Careful monitoring of urinary output is necessary, and caution should be taken to avoid overhydration. Relapse and death, after initial recovery, have been attributed to incomplete gastric emptying and delayed absorption.

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North Carolina Medical Journal

Features for Patients

May 1984

The Patient Has a Sore Throat. What Should the Patient and Doctor Do?

Floyd W. Denny, M.D.

Upper respiratory infections, including sore throats, are the most common reason for visits to physicians in the United States.¹ The number of upper respiratory infections suffered by patients varies with age. During the first few years of life, children have 6 to 8 upper respiratory infections per year, depending on their exposure to older children and adults. This number decreases with each year of life; by school age the child will have 5 to 6 upper respiratory infections per year, and adults will have 3 to 4 per year.² Most of these infections are mild and require no medical attention, but a proportion are severe enough for the patient to seek medical care. This makes the problem of upper respiratory infections a major consideration in the delivery of medical care.

Viruses are the most common cause of upper respiratory infections and are thought to be responsible for over 85 to 90% of these illnesses.² Group A beta-hemolytic streptococcus (beta strep) has been considered for years the most important bacterium that causes upper respiratory infections. A recent study suggested that two other bacteria, *Mycoplasma*

pneumoniae and *Chlamydia trachomatis*, may cause sore throats in adults, but this report is too preliminary to warrant any changes in the care of patients with upper respiratory infections.³ Other bacteria such as *Haemophilus influenzae* and *Streptococcus pneumoniae*, although important in such infections as pneumonia and otitis media (earaches), have not been shown to be important causes of upper respiratory infections. This means that the primary care physician is faced with the problem of deciding which of those patients with an upper respiratory infection has a viral infection for which there is no specific treatment and which has a streptococcus infection which can be treated with an antibiotic.

There are several reasons for treating patients with streptococcal upper respiratory infections (strep throat). The most important is that such treatment prevents the occurrence of rheumatic fever. Rheumatic fever that occurs after the symptoms of sore throat have subsided may affect the muscle or valves of the heart. Treatment also eradicates the streptococcus from the throat, thus preventing it from spreading to others or causing infections in other parts of the body, such as in sinuses, ears or lymph nodes. These complications occur in such a small number of patients that

treatment just to prevent them is probably not warranted. Many people believe that treatment of strep throats results in rapid relief of symptoms, but controlled studies have shown that this is true only if the treatment is given very early during the infection (first 24 hours).⁴ Even under this circumstance the time that the illness is shortened is limited because strep throats usually last only 3 to 5 days in patients who receive no treatment. Thus, the primary reason for treating strep throats in the past has been to prevent rheumatic fever.

At one time rheumatic fever was a very common and feared disease, but in the past few decades it has occurred so infrequently that many physicians rarely see cases. This apparent disappearance of rheumatic fever has presented several problems to physicians. Has rheumatic fever really gone away and if so, why? If rheumatic fever is no longer a problem, then how should the patient with a strep throat be managed in 1984? Patients are also faced with certain questions in this regard: When should they seek medical care for an upper respiratory infection or sore throat? Are sore throats a serious problem for them today? These complex issues were the impetus for a conference held in February 1983 and sponsored by Ross Laboratories,

From the Department of Pediatrics, University of North Carolina School of Medicine, Chapel Hill 27514.

Illustrations by Ernest Craigie, M.D.

the American Heart Association and the National Institute of Allergy and Infectious Diseases of the National Institutes of Health entitled "Management of Pharyngitis in an Era of Declining Rheumatic Fever."⁵ This article summarizes my interpretation of the results of that conference, including the management of sore throats in 1984.

Rheumatic Fever Is Disappearing in Developed Countries. Why?

Rheumatic fever is not a disease that has to be reported, so accurate figures on its occurrence are not generally available. At the conference comprehensive studies from Baltimore and Memphis confirmed the widely-held impression that the incidence of rheumatic fever has declined in the past few decades and is now rarely seen by most physicians. Since the conference, a report from Rhode Island has confirmed the decline in that state.⁶ The decline appears to be true for industrialized countries, but rheumatic fever remains a significant problem in developing countries.

Dr. Leon Gardis presented data which suggested that treating strep throats is responsible, at least in part, for the decline in rheumatic fever. This observation is of great importance because the incidence of rheumatic fever appeared to be declining before antibiotics were available. The observation is also important because it dictates that we should continue to treat strep throats to prevent rheumatic fever. The big question that remains for the physician in 1984 is whether the management of sore throats should be changed in any way. Likewise, the patient or the parent of the patient must decide whether or not a sore throat requires a visit to the doctor.

Ways to Diagnose Strep Throats

The physician has three sets of tools to employ in deciding which patients with a sore throat have a strep infection: (1) the usual epidemiological behavior of strep infections, (2) the

clinical manifestations in the patient and (3) help from the laboratory. Strep throats are most common in children 5 to 10 years old and are unusual in children under 2 years of age and in the elderly. Their occurrence in adolescents and young adults is dictated primarily by situations that increase contact, such as schools or the military. Streptococcal infections have a definite seasonal preference for winter and spring. They are also associated closely with crowding, and are seen more commonly in such groups as school children and the poor. The classical symptoms and signs of strep throat are its abrupt onset, sore throat (pain on swallowing), fever, exudate (pus) on the tonsils, tender and enlarged lymph nodes in the neck and the occasional rash of scarlet fever. Find-

ings that suggest a diagnosis other than strep throat are a runny nose, cough and vomiting and diarrhea (except in the young child). Unfortunately, the classic findings of strep throat do not occur in all infected patients; studies have shown that two-thirds or less of cases can be diagnosed accurately by these epidemiological and clinical methods. For the accurate diagnosis of strep throat help from the laboratory is essential.

A variety of laboratory tests has been used to help diagnose strep throats. Some of these are non-specific, such as the number of white blood cells or the erythrocyte (red blood cell) sedimentation rate; none has proved to be an effective tool so these tests are not used generally. The determination of antibodies to





The time-honored way to demonstrate strep in the throat is by a throat culture.

A properly obtained and properly processed throat culture will reveal streptococci in about 90% of strep throat cases. People with untreated strep throats will continue to "carry" the streptococcus in their throats for several weeks or even months after the acute illness. Fortunately, after a short time the streptococci that are carried in this way do not seem to harm the carrier and do not spread readily to others. On occasion, though, this carrier state poses a problem to the physician in interpreting throat culture results. In these cases the doctor must assess the clinical and epidemiological findings and make a decision regarding the significance of the positive throat culture.

Making the Diagnosis

The physician makes the final diagnosis of a strep throat using all available tools — epidemiological data, clinical findings and the throat culture. Because of the cost of a throat culture, much effort has been expended in developing methods that help physicians decide which patients with sore throats are likely to have a strep throat and thus should have their throats cultured. These management plans or protocols

(called clinical algorithms) are based on studies showing the percent of patients with certain epidemiological and clinical findings who have a positive culture. For example, the child under 2 years of age with fever and a runny nose almost certainly doesn't have a strep infection and need not be cultured. Also, the adult with a cold and cough is unlikely to have a strep throat and should not have a culture.

Physicians are encouraged to use available clinical and epidemiological methods in an organized way in the management of patients with sore throats. A few patients, such as those with a history of previous rheumatic fever, those with scarlet fever or those who are more severely ill, can be treated immediately. In such cases the throat culture can be used to confirm the diagnosis. Patients who are considered to be at high risk for a strep infection because of the epidemiological and clinical findings should be cultured and only those with positive cultures should be treated. On occasion the physician may start the patient on an oral antibiotic while awaiting throat culture results. If the culture is negative, the antibiotic should be discontinued.

In the past when rheumatic fever was more of a problem, throat cultures were used extensively to identify people with positive cultures who would then be treated. It is the feeling today that these extreme efforts are no longer necessary or even advisable. For instance, it is no longer recommended that family contacts of sore throat cases be cultured unless they are symptomatic. Throat cultures following treatment to detect treatment failures are no longer recommended if the patient no longer has symptoms.

Treatment

Specific. Penicillin remains the drug of choice for treating patients with strep throats unless they are allergic to it. A single injection of a long-acting penicillin (benzathine penicillin) is the preferred and most

the group A streptococcus in the blood is an excellent and reliable way to make a diagnosis, but is not used frequently because the test requires a comparison between blood drawn at the time of illness and blood drawn 2 to 3 weeks later, which precludes its use to diagnose acute disease. The only reliable way to diagnose an acute strep infection is to demonstrate the streptococcus in the throat. The time-honored way to do this is by a throat culture. Since the throat culture requires 18 to 24 hours before results are known and is relatively expensive, efforts have been made to find other ways to demonstrate the streptococcus in throats. None of these has been developed to the point that it is satisfactory for clinical use, so the throat culture remains the method of choice.

... rest, fluids, soft diet.



reliable treatment. Because this shot can be painful, many physicians prefer to use oral penicillin instead. This is satisfactory therapy if the penicillin is taken as directed for a full ten-day period. The big problem with oral medications is that patients tend to forget them after they feel better, which usually occurs with strep throats after two to three days.

For the patient who is allergic to penicillin, oral erythromycin is the antibiotic of choice. For the rare patient who cannot tolerate either of these two drugs an oral cephalosporin or clindamycin can be used. Ten days of therapy are necessary for all of these oral medications. The sulfonamides and tetracycline drugs do not eradicate strep from the throat and are not acceptable forms of therapy.

Non-specific. Patients with strep throats also benefit from non-specific treatment. Rest is essential and some patients may need to stay in bed for several days. Sufficient fluids to prevent dehydration should be encouraged and the patient can have a soft diet as tolerated. Aspirin or acetaminophen can be used to relieve the pain of sore throat or painful lymph nodes. Gargles with a warm salt solution may help relieve the painful throat. Because of the commonness of strep throats, nothing is gained from

isolating the non-hospitalized patient with a strep throat. Children can return to school and adults to work as soon as they feel well enough to do so.

The Cost of Sore Throats

Because upper respiratory infections are so common and the cost of medical care so great, much attention is being paid to the most economical way to manage patients with sore throats while maintaining good standards of medical care. Physicians are encouraged to use clinical algorithms so that their care of these patients is standardized at all times. Algorithms are especially useful for nurse practitioners and other allied health personnel who are assuming primary medical care in some areas. Terms such as "cost-effectiveness analysis" and "cost-benefit analysis" are being used to describe efforts to develop the best treatment at the least possible cost. Because our knowledge about strep throats and rheumatic fever is in a state of great flux, there is no consensus about the only way to manage sore throats. The rules outlined above appear to be the best that can be offered today, but changes will almost certainly occur in the future.

What Does the Patient Do?

It is not easy for patients, or parents

of patients, with sore throats to know what to do when the situation is so complex. Probably the most important thing for the patient to know is that rheumatic fever is no longer the problem that it once was in the United States. This is leading to a change in the strategy for managing sore throats, with a relaxation of some of the former vigorous efforts used to diagnose and treat strep throats. The move to reduce medical care costs has accentuated the importance of these efforts. In this climate the patient must remain in close communication with primary care physicians, so that mutually satisfactory management of sore throats in 1984 can be attained.

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Vitamins

Jim Worden, Pharm.D.

American consumers spend over three billion dollars a year on vitamin and nutritional products. Does this mean that diet supplementation and better health go hand in hand? No, not necessarily; in most cases, the American diet does not need supplementation. Most health authorities agree that attention to a balanced diet and adequate caloric intake eliminates the need for supplemental vitamins for most people.

Another segment of the American public seeks vitamin therapy for relief or cure of such illnesses as cancer, heart disease, and arthritis. Again, very few of these people will derive much benefit from such therapy. Misconceptions surrounding vitamin use are both plentiful and varied. This article reviews the actions of the different vitamins, the disease states associated with their deficiencies, the recommended daily intake of these nutrients, and identifies those individuals more prone to require vitamin supplementation.

Vitamins are chemically unrelated organic substances that play an essential role in the chemical machinery of the body. They are materials so universally available in diets that humans no longer have (or need) the ability to synthesize them. By definition, vitamins must be chemicals supplied from external sources.

Most people eating a balanced diet do not need to take vitamin pills. Normal persons can develop vitamin deficiency by eating peculiar diets, but you have to work hard to become deficient. Vitamins play such a specific role in body function that a deficiency in a specific vitamin results in a specific disease with resultant disability or even death. For example, a

deficiency in vitamin C can result in scurvy, a rare disease in the U.S., but one that could result in death if left untreated. Healthy people do not need to have their diet supplemented by vitamins. Sick persons may or may not need supplementation.

Generally speaking, vitamins can be grouped into two distinct categories: (1) fat-soluble vitamins which include A, D, E and K and (2) water-soluble vitamins B, C, niacin, and folic acid. Other vitamins such as pantothenic acid, biotin, choline, and the bioflavonoids will not be discussed as their nutritional significance is not as well understood.

Fat Soluble Vitamins

Vitamin A (retinol) is necessary to prevent night blindness and drying of the conjunctiva, the mucous membrane that covers the eye. Worldwide, vitamin A deficiency is a leading cause of blindness in childhood. Pregnant women must take in enough retinol to avoid fetal malformations. Since vitamin A is a fat-soluble vitamin, most fatty foods contain it; fish, organ meats, cream, butter, eggs and milk are all excellent sources. Retinol is also available in carrots, squash, and dark leafy vegetables.

In the U.S., vitamin A deficiency occurs more often from an inability to absorb fat properly than from a deficient diet. Certain diseases such as cystic fibrosis and cirrhosis, and certain drugs such as cholestyramine, can cause fat malabsorption and consequently vitamin A deficiency. The U.S. recommended daily allowance for vitamin A in adults is 5,000 I.U. and 8,000 I.U. in pregnant or breast-feeding women. High doses of retinol should only be taken under close medical supervision. Vitamin A is

stored in the body and high doses can lead to a toxic state with throbbing headaches, nausea, vomiting, dizziness, insomnia, and night sweats.

A promising yet largely investigational use of vitamin A derivatives has been in the prevention of certain cancers and skin disorders. Doses of vitamin A required to attain these benefits, however, are also high enough to cause toxicity.

Vitamin D is necessary to stimulate the absorption of calcium from the small intestine and, in conjunction with other body hormones, to regulate the concentration of calcium in the serum. Vitamin D can be synthesized if the skin is irradiated with sunlight. If sun exposure is insufficient, though, vitamin D must be obtained from the diet.

Deficiency of vitamin D in children can lead to rickets, a disease characterized by soft bones and deformed joints due to a lack of adequate calcium in the bone. The adult disease equivalent to rickets is osteomalacia, an equally debilitating disease seen in patients with kidney disease, malabsorption syndromes or other endocrine problems.

Milk and milk products are the major sources of vitamin D in the U.S. diet. Other rich sources include eggs and fish. Most people obtain the recommended daily allowance of vitamin D in their diet and from exposure to sunlight. Adults should limit their intake to 400 I.U. per day. Doses greater than 1,800 I.U. may inhibit growth in infants. Symptoms of an overabundance of vitamin D include anorexia, weakness, nausea, vague aches, weight loss, hypertension, anemia, and possible irreversible kidney failure. Patients who feel they need additional vitamin D should seek the advice of their physician or pharmacist.

From the Department of Pharmacy Services, Pitt County Memorial Hospital, Inc., Greenville 27834.

Vitamin E. Although the biochemical function of vitamin E is still unclear, it is thought to protect vital membranes from oxidative damage. There appears to be no well defined vitamin E deficiency state in adults and, since infant formulas are supplemented with vitamin E, an infant deficiency condition is also rare. Foods rich in vitamin E include green vegetables, whole grains and margarines.

The U.S. recommended daily allowance for vitamin E is 30 I.U. for adults, 10 I.U. for children and 5 I.U. for infants. An average American diet provides 15-20 I.U. of vitamin E. Of the fat-soluble vitamins, vitamin E appears to be one of the least toxic in large amounts, although it is important to watch for interactions with anticoagulants and iron products. Claims for megadose vitamin E therapy improving circulatory disorders, heart diseases, and athletic and sexual performance are largely unfounded.

Vitamin K. Green leafy vegetables, dairy products, and fruits constitute the major dietary sources of the fat-soluble vitamin K. But most vitamin K is produced by microorganisms in the intestine. Bleeding is the most common symptom of vitamin K deficiency and it is usually associated with a serious illness. Occasionally, a vitamin K deficiency is seen in a person who takes antibiotics that may inhibit the organisms responsible for vitamin K synthesis. However, this is only seen if dietary intake is insufficient. Other possible inhibitors of vitamin K absorption include liver disease, malabsorptive syndromes, and drugs such as cholestyramine resin, mineral oil and oral anticoagulants.

Very few of the over-the-counter vitamin preparations contain vitamin K. There is no recommended daily allowance for the vitamin, but a daily intake of 70-140 mcg is considered safe and effective. Normal U.S. diets contain 300-500 mcg of vitamin K per day.

Water-Soluble Vitamins

Vitamin C (ascorbic acid). As mentioned earlier, vitamin C is necessary to prevent scurvy. Scurvy causes impairment of wound healing and is manifested early on by anorexia, weakness and joint and muscle aches. Bleeding into the skin, muscles, joints, gastrointestinal mucosa, and major organs can also occur. Death may occur if the disease is left untreated. In infants, ascorbic acid deficiency may cause retarded growth and development, as well as anemia and hemorrhaging.

Fresh fruits and vegetables are good sources of vitamin C, and a normal diet contains several times more than the 10 mg/day vitamin C needed to prevent scurvy. The U.S. recommended daily allowance for ascorbic acid is 60 mg for adults, 40 mg for children and 35 mg for infants.

Vitamin C has been used for other medicinal purposes. Although reports that vitamin C prevents colds have been made for some time, well-controlled studies have failed to show a significant benefit. Given in large doses (1-10 gm), ascorbic acid is generally safe; however, significant interactions may occur with drugs or lab tests. Urine glucose tests may give false readings if given while the patient is taking megadose vitamin C. In addition, the actions and/or toxicities of several antibiotics, including the sulfo drugs, may be affected by ascorbic acid. You should consult your pharmacist or physician to determine whether ingestion of large amounts of vitamin C will have an effect on medications or tests you may be using.

Vitamin B-1 or thiamine is required for both carbohydrate metabolism and nervous system functioning. Beriberi, the thiamine-deficiency state, is rare in the U.S. but occurs in areas where polished rice is the major ingredient of the diet. Heart failure, swelling, weakness, and numbness in the fingers and toes constitute

possible symptoms of this disease. Infantile beriberi may also occur, mimicking the picture of meningitis. A more common presentation is in an alcoholic whose diet is unbalanced. A severe metabolic condition (Wernicke-Korsakoff syndrome) may be seen in this type of person. Psychosis, permanent neurologic damage and even death can result if this syndrome is left untreated.

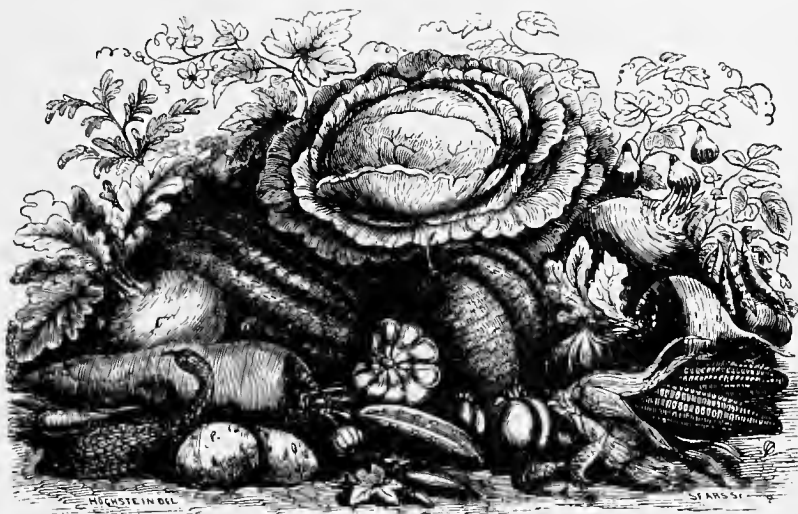
The recommended daily allowance of thiamine is 1.5 mg for children over 4 and adults, 0.7 mg for children under 4, and 1.7 mg for women during pregnancy and lactation. Excessive thiamine is rapidly eliminated in the urine and is relatively safe, as are many of the water-soluble vitamins.

Riboflavin (vitamin B-2) is involved in numerous reactions necessary for cellular growth and metabolism. Symptoms of this deficiency include inflammation of the skin over joint areas, scaling of the lips and mouth and inflammation of the tongue. This may progress to a generalized dermatitis over the rest of the body.

Sources rich in vitamin B-2 include eggs, fish, meat, liver, whole grains and milk. The U.S. recommended daily allowance for this vitamin is 1.7 mg for adults and 2 mg for pregnant or lactating women. Excess riboflavin is excreted in the urine.

Niacin and niacinamide are vitamins that are necessary components of the cellular respiratory system. Humans synthesize about half their niacin from the amino acid tryptophan. The other half must be supplied from their diets. The once common disease, pellagra, which is the niacin deficiency state, is now rare in this country. It is still seen in alcoholics, the elderly, and those on unusual diets. This disease is characterized by the "3 Ds": diarrhea, dementia and dermatitis.

Lean meats, liver, fish, whole grains, green vegetables, and legumes are foods high in niacin content. The recommended daily allow-



ance of niacin is 20 mg. High doses can cause serious side effects. Gastrointestinal irritation, cardiac arrhythmias, impaired liver function and facial flushing can be associated with high doses of niacin. Niacinamide does not produce the flushing that comes from the use of niacin. High dose niacin is used to lower the concentration of cholesteral and triglyceride in the plasma.

Vitamin B-6 or pyridoxine is necessary for the metabolism of amino acids or protein in the body. In infants pyridoxine deficiency is manifested by convulsive disorders and irritability. Adults show the same signs and symptoms as they would with niacin and riboflavin deficiencies (dermatitis, neurological defects).

Foods with a rich supply of pyridoxine include meats, nuts, bananas, potatoes and cereals. Most U.S. diets provide the recommended daily allowance for vitamin B-6, which is 2 mg for those over 4 years of age, 2.5 mg for pregnant or lactating women, and 0.7 mg for children under 4 years old. Pyridoxine is generally considered nontoxic.

There are several noteworthy drug interactions possible with pyridoxine.

The anti-tuberculosis drugs isoniazid and cycloserine, as well as the blood pressure medication hydralazine, can antagonize pyridoxine to some degree. On the other hand, pyridoxine may reduce the therapeutic effect of levodopa, a drug for people with Parkinson's disease, if both are taken. If you are taking any of these drugs, consult your pharmacist or physician to determine if they might interact with pyridoxine.

Cyanocobalamin or vitamin B-12 is required for the metabolism of fats, for cell division, and for recycling other necessary vitamins such as folic acid. A deficiency in this vitamin can result from a defect in absorption or from inadequate intake of the vitamin. A deficiency of B-12 causes the clinical picture we call pernicious anemia. Because the body conserves and stores this vitamin, the deficiency state may require many years to develop.

Animal protein is the largest contributor of vitamin B-12 content in the diet. Small amounts may also be found in legumes such as peas and beans. Because of the lack of B-12 in vegetables, vegetarians who consume no meat at all are at a risk of

developing a deficiency state and should consider supplementing their diets with vitamin B-12. The U.S. recommended daily allowance is 2 mcg for infants, 3 mcg for children, 6 mcg for adults, and 8 mcg for pregnant or lactating women. Vitamin B-12 has little therapeutic benefit except in people deficient in the vitamin. Even in large doses this vitamin possesses little toxicity.

Folic Acid. In the body folic acid serves approximately the same function as vitamin B-12. In particular, folate is important in the biosynthesis of required components of cells. Vitamin B-12 is necessary for the regeneration of folic acid in the body. Therefore vitamin B-12 deficiency can result in folate deficiency which presents the same way as vitamin B-12 deficiency with mouth irritation, diarrhea, nervous system manifestations, and anemia. Causes of this deficiency are also similar to those of B-12 deficiency (poor diet, alcoholism).

Foods with high folic acid content include fresh vegetables, liver and organ meats. As with other vitamins, cooking, canning or long exposure to heat may destroy much of the vita-

min content. The U.S. recommended daily allowance for folic acid is 0.1 mg for infants, 0.2 mg for children, 0.4 mg for adults and 0.8 mg for pregnant and lactating women. Toxicity with folic acid is almost nonexistent.

As with several other vitamins, there can be significant interactions between folate and certain drugs. Methotrexate (a cancer drug), phenytoin (an anticonvulsant), oral contraceptives and trimethoprim (an antibiotic) may all cause antagonism of folic acid in the body. In addition, folic acid may reduce phenytoin concentrations. Consult your health professional if you have questions about any drug interactions with folic acid.

In summary, most vitamins fulfill a very specific role in the maintenance of normal body function. The amount of vitamins needed is small and an increase in the vitamin intake beyond what is required to carry out the specific function results in no ben-

efit. Moreover, their deficiency causes very specific symptoms in areas of the body most dependent upon that vitamin and it is easy to determine that the person is not healthy. Fortunately, these deficiency states are not seen frequently in the United States, most likely because Americans have a dietary intake adequate in vitamin composition. There are certain segments of the population, however, who are known to be at risk for vitamin deficiencies unless vitamin supplementation is added to their diet. These include the following categories:

1. Increased metabolic requirement: pregnancy, lactation, infants, severe injury, major surgery, and severe infection.
2. Poor absorption: prolonged diarrhea, severe gastrointestinal disorders, malignancies, cystic fibrosis, etc.

3. Inadequate dietary intake: the aged, alcoholics, and the impoverished.
4. Other: patients on certain drug therapy such as oral contraceptives, selective antibiotics, etc.

Selection of a multivitamin for people who fall into the above groups should be based on attempting to supply approximately 100% of the recommended daily allowance for each vitamin needed. Remember, excessive doses or higher potency brands will not offer any additional benefit, can cause toxicity (especially the fat-soluble vitamins) and usually will be more expensive than conventional supplemental vitamins. Vitamin supplementation is not a substitute for a well-balanced diet.

Editor's Note: My wife and I have enjoyed and are enjoying life. Savings from not purchasing vitamins or cigarettes contribute to our happiness.

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Investment Advice to the Fairest of the Fair The Perspective of an Ophthalmologist

Banks Anderson, M.D.

Frankly this is a racist prospectus. It is targeted at Caucasians of north European stock but others may read it and chuckle at paleface absurdities. It begins with a fairy tale:

Once upon a time, there lived the most beautiful of women, the fairest of them all. Her lips were red as the ruby, her hair black as the raven, her skin as white as the new fallen snow, her name Snow White.¹ For centuries swains were enraptured by such snowy whiteness tinted only with the rosy blush of modesty. Needless to say every belle did her best to preserve this purity of complexion. Wide brimmed hats, long sleeved blouses, shoe top dresses, even gloves were summertime garb. Many even carried head shading parasols . . . those that could.

Many could not. Before 1850 the economy was agricultural. The poor worked the fields sun-up to sun-down, especially when the sun was high in the growing season sky. An athletic tan could only be avoided by wealthy ladies who had no need to brave the mid-day sun with mad dogs, the poor, and a bumpkin English squire or two. The ambiance of affluence dictated the allure of the pallid epidermis. Too often the poor were semi-starved and gaunt while the aristocracy ate well; pleasing plumpness and rotundity were also hallmarks of the leisured classes. Rubens painted the sexiest of women, well upholstered roundness in snow white skin, and the males of the day hung these ideals in their billiard rooms and salons. Nail-ups as it were.

What so changed the ideal woman? Why is now the thin, tanned, athletic body with sun-bleached hair in such vogue? You have, no doubt, guessed. The allure of affluence again. In the twentieth century where does the wage slave work? Indoors. Where do the affluent go in the winter? Palm Beach, Cancun, Aspen, St. Moritz. Now the stigma of wealth is the brown body while the working class has moved out of the fields and into factories and offices. Their former nut-brown countenances now become snow white and their derrières rotund from tending their indoor stations. The poor pallid things seek out water reflections, arrange aluminum panels, shed every scrap of clothing the law permits, abandon the hat (even in the cathedral) and otherwise do their best to obtain the tanned allure of affluence. But what a price!

Malignant melanoma of the female leg, almost unknown before, now appears.² Carcinomas of the face and arms become the commonest cancer.³ Dermatologists and plastic surgeons busily freeze, tuck, and lift attempting to repair their sun-rovoged visages. Worn old before their time, the wrinkled splotched faces of these Sun Browns thicken and sag from actinic elastic tissue damage and grow excrescence after excrescence attempting to repair the irreparable. Snow White knew that apple or no, her prince would come and kiss her smooth pure-white face. Today's older Sun Brown may find that today's prince possesses by her mottled wotted cheek and seeks a younger smoother one instead.

If beauty is only skin deep, and is

valued, why then should we parents tolerate our twelve year olds frying their skins, basking like lizards at the pool or beach? There is nothing in-born or even rational about the fickle Caucasian male's current preference. When computers run our factories and the masses are turned out again to the streets and fields while monogermers and directors operate their indoor data terminals, Snow White may once again become the epitome of skin deep beauty. Girls, this may come sooner than you think, so save your skins! Protect your investment!

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From Duke University Eye Center, Durham 27710.

SWEAT OR NO SWEAT

Peter W. Heald, M.D., Claude S. Burton, M.D., and J. Lamar Callaway, M.D.

"Horses sweat, men perspire." This well-known adage demonstrates our peculiar relationship with sweating. Sweat is essential to our everyday life. Yet we try to refine it with fashionable terms, cover it with fragrances, desiccate it with powders, cushion it with Odor Eaters, feminize it with Secret, masculinize it with Right Guard, only to work up a sweat during our hours of relaxation.

Our skin produces two types of sweat. One of these is called eccrine sweat which is produced over the entire body surface. This is distinct from the second type, known as apocrine sweat, which is produced in the underarm area, the groin, and rarely elsewhere. The sweat glands that produce these two types of sweat differ in their structure, function, and final product. Eccrine sweat is clear fluid readily produced in response to heat or emotional stimuli. These glands continually produce sweat and can achieve production rates on the order of quarts in athletes during a workout. Apocrine sweat, however, is a cloudy, thicker material that is more adherent to the skin. Apocrine sweat contains more materials such as iron, fats, and a fatty substance known as lipofuscin. Many bacteria thrive on the material in apocrine sweat. Also the apocrine glands cannot continually produce sweat. After a gland is emptied it sometimes takes up to a day to reload with apocrine sweat.

Eccrine sweat functions primarily to cool the body and maintain a minimal amount of hydration for the skin. These are benefits that go large-

ly unnoticed during the course of a day. However, when these sweat glands are overproducing they are quickly noticed.

Excessive sweating, known as hyperhidrosis, can be disabling although it is rarely due to a specific disease. Hyperhidrosis is defined by our perception of how much sweat is needed. Perhaps the body senses the need to sweat before we can consciously appreciate this. In many cases, such as in the course of a fever, it is appropriate to have hyperhidrosis. Nonetheless at times the body reacts as if there is reason to sweat, eccrine sweating is triggered and our various anti-perspirant routines begin.

If the sweating is not symptomatic enough a patient may present with a problem that is actually a complication of excessive eccrine sweating. Fungus and yeast infections of the skin occur in excessively moist areas such as the feet or in the groin. Failure to control excessive moisture will lead to more frequent recurrences and slower clearing of these infections. Excessive sweating over the trunk may lead to the production of miliaria (prickly heat). This was frequently found in our troops in Vietnam. Not only is this produced by excessive sweating but it is also contributed to by external pressure on the sweat glands. In Vietnam this may have been due to carrying backpacks and other equipment. In the hospital miliaria is frequently seen on the patient's back, especially during prolonged bedrest and fever.

Another, although infrequent, complication of sweating is contact dermatitis. Many people would not realize that they are allergic to an elastic in their underwear or a cloth-

ing dye in their underclothes were it not for the eccrine sweat which washes into this material and washes the allergic material out and onto the skin where the dermatitis then occurs. Again, controlling sweating in this setting helps in managing the patient. While eccrine sweating has little to do with eczema of the hands and feet, the latter disorder still goes by the name dyshidrosis (abnormal sweating). Indeed, patients with this condition often have excessive eccrine sweating along with their hand or foot eczema. This over-reactivity of the sweating system is analogous to the over-reactivity of their skin which can be irritated by all but the mildest of soaps and lotions.

The approach to treating hyperhidrosis is one of trial and error. Several agents are very good at absorbing the extra sweat, and for many patients this will suffice: a drying powder such as Zeasorb is very good when applied to the areas being drenched on a regular basis; for the feet, pads such as Odor Eaters are also absorbent.

One home remedy that has been successful for people who excessively produce sweat is to use tepid tea in a bowl to soak the hands, feet, or whatever part is bothered by the hyperhidrosis. Do this for approximately twenty to thirty minutes twice a day. There is an agent in the tea which clogs sweat glands.

Two agents that have been used to clog up sweat glands are the aldehydes (gluteraldehyde and formaldehyde) and aluminum chloride. These agents must be prescribed and applied under the guidance of a physician because many reactions can occur in the inexperienced user. Bath of these products coagulate pro-

From the Department of Medicine, Duke University Medical Center, Durham 27710.

tein in the sweat ducts leading to a blockage of the duct and a consequent decrease of sweating. The glutaraldehyde has a side effect of making the skin it is applied to turn dark.

While most patients may actually believe that there is a pill that could be taken for sweating, this is not the case. Probanthine is a medication that has had a very unpredictable response. Some patients may take this medicine and hardly sweat again whereas others seem to be untouched by it. In those who do have an effect there are also the side effects of dry mouth and flushed face.

The latest form of therapy for sweating is the iontophoresis machine. This is a machine that passes a direct current through the skin and in that process somehow damages the sweat ducts. These machines run from \$100 to \$300 and may be purchased by the physician or patient. Treatments typically are conducted three times a week, and after two or three weeks the patient can be relatively sweat-free in the area

treated with the iontophoresis machine for up to two months. The current generator is plugged into the wall outlet and a pan of tap water is hooked up to the machine. The patient then places the part of the body to be treated into the pan and the machine is turned on. For tough to treat areas there have been adaptations made such as wiring a brass door knob which can then be placed into the area (the underarm, for example) for delivery of current. It is not clear why this type of treatment works since the sweat glands appear unchanged. However, it has been well-documented that this does decrease sweating.

The most popular type of sweating is that of apocrine sweating. The reason apocrine sweating is the subject of so many television advertisements is its ability to produce a foul odor. Apocrine sweat itself does not smell but bacteria grow readily in the rich materials found in the sweat. The bacterial products are responsible for the odor and all of the embarrass-

ment that this brings. In people with excessive eccrine sweating there is usually a minimal problem with apocrine sweat odor. This is because the eccrine sweat effectively cleanses the underarm by drenching it with the clear fluid which washes away the bacterial products.

Because the bacteria are necessary for apocrine sweat odor, antibiotic agents have a role in the management of problems related to apocrine sweating. Topically applied Clindamycin, Tetracycline, and Erythromycin have all been noted to decrease bacterial counts and improve underarm odor in the general population. The most common commercial agent used for underarm perspiration is aluminum chloride, which leads to blockage of the sweat glands and decreased sweating. Excessive underarm sweating is most likely due to eccrine sweat, and other agents used in eccrine sweating disorders may also be useful: the drying powder, glutaraldehyde, and iontophoresis.



IT'S GETTING TOUGHER FOR NANCY RAY TO BE A MOTHER.

Nancy Ray has multiple sclerosis.

Every day it becomes harder for her to see. Harder for her to walk. Harder to do the things she wants to do for her family.

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Multiple sclerosis destroys the myelin covering that surrounds nerve fibers in the brain and spinal cord. Messages to and from the brain get lost as they travel through the damaged area. So your eyes, arms, legs don't do what you want them to do.

MS can be mild. Or it can be severe. Once you've got it, you've got it for life. Most days, Nancy Ray can get around with a walker. With a lot of time and effort, she can even prepare meals for her family. Some people with MS aren't that fortunate.

The National Multiple Sclerosis Society is helping people with MS live with MS. And funding research for a cure, all over the world. We can do it, but only with your help.

Please give generously. It's tough enough to be a mother without MS.

**NATIONAL
MULTIPLE SCLEROSIS
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New York, New York 10017

JUST WHEN YOU'RE STARTING TO LIVE, MS CAN STRIKE

Mimi, Violetta and The "Captain of All The Men of Death"

INH (Isoniazid) Poisoning

Ronald B. Mack, M.D.

CERTAINLY one of the major medical advances in the last half of the 20th Century has been the discovery of medications to combat one of the scourges of mankind — tuberculosis. This disease has been euphemistically referred to by many names throughout history, e.g., the "white plague," "consumption," etc., but my favorite is the name given to tuberculosis by John Bunyan. Mr. Bunyan, many of you will recall from English Lit 101, was the 17th Century British author who wrote *The Pilgrims Progress*. This famous writer referred to "consumption" as "the caption of all the men of death" and this beautiful description is still being used in our century. It was not until 1882 that Robert Koch isolated the tubercle bacillus. Thus before that time writers had to invent names to refer to this disease in very descriptive terms to imply its deadliness.

The great doctor-essayist Lewis Thomas in his recent book, *The Youngest Science: Notes of a Medicine Watcher*,¹ describes his own medical school training in this country between the two world wars and reminds us that the "two great hazards to life" in those days were tuberculosis and tertiary syphilis. He further relates that "these were feared by everyone, in the same way that cancer is feared today." Probably some of you remember the manner in which tuberculosis was treated before World War II — the sanatoria, the mountain resorts, fresh air, sunshine, nutritious diets — hoping and waiting for the body to heal itself. If these methods failed one often resorted to iatrogenic lung collapse (obviously only for pulmonary TB) utilizing induction of pneumothorax, or rib removal over the affected area, or my absolute favorite — plombage — the implantation of methylmethacrylate balls (like ping-pong balls). We've come a long way, baby!!

Since the early 1950s we have been able to use isoniazid (INH) in the battle against the "captain of all the men of death." INH remains the cornerstone of the treatment for active tuberculosis as well as the drug of choice for prophylaxis therapy of positive TB skin test reactors. INH, as helpful a drug as you can imagine, is a bad dude if taken in overdose. The morbidity and mortality following major INH overdose are very significant indeed. (By the way, lest we forget, tuberculosis is not a disease only of the past; this disease and malaria are the most widespread and persistent human infections in the world at large even as we speak.)

From the Department of Pediatrics, Bowman Gray School of Medicine, Winston-Salem 27103.

When INH is ingested therapeutically it is rapidly absorbed, primarily in the small intestine, and produces peak plasma concentrations in 1 to 2 hours. It is important for our purposes to recall that INH significantly penetrates the CNS. The most important pathway quantitatively for INH metabolism involves *acetylation*. (Is this biochemistry really necessary?) Just as you can divide all children into two groups — those that like peanut butter and those that don't — you can divide INH acetylators in two groups — *slow* and *fast*. Your individual acetylator status is genetic. *Slow acetylators* are homozygous for the regressive gene and have an INH half-life therapeutically of 2-4 hours whereas *rapid acetylators* are either heterozygous or homozygous for the dominant gene. The INH half-life for rapid acetylators is 0.7-2 hours. About 60% of all Caucasians and blacks are slow acetylators whereas about 90% of orientals and Eskimos are rapid acetylators. It is probably better to be a rapid acetylator if you accidentally overdose on INH. Isoniazid has a volume of distribution (V_D) of 0.6 l/kg and has negligible protein binding.

INH is dispensed in tablets of 50, 100 and 300 mg. As little as 1.5 grams taken acutely can cause toxicity in an adult (Gosh, that's only five 300 mg tablets!!). Acute ingestion of 6-10 grams by an adult (20-30 of the 300 mg tablets) can cause severe toxicity and even death. Ingestion of 15 grams or more acutely by an adult is often quite fatal if untreated.

The clinical triad of isoniazid overdose consists of *repetitive seizures*, *metabolic acidosis* and *coma*. The clinical features of an acute INH overdose begin as early as 30 minutes after ingestion or as late as 120 minutes (for a few, up to 4 hours post ingestion). *The initial signs and symptoms* are quite non-specific, namely: nausea and vomiting, dizziness and blurred vision, ataxia and increased deep tendon reflexes. Rather quickly the patient can lapse into coma and experience repetitive seizures (generalized or focal) and then again quite rapidly progress to intractable coma and death by respiratory or cardiac failure. Hyperpyrexia is a common feature. Severe hypotension, oliguria or anuria can also occur.

Without question, the *convulsions* and the *metabolic (lactic) acidosis* are the most dramatic systemic effects of INH overdose. The seizures are frightening and typically quite repetitive. The alleged cause of the seizures is a fascinating story, at least to me. (But then I am fascinated

by the chromosome status of Grammy Award Winners.) One of the neurotransmitter systems that holds us together involves the proper functioning of the glutamic acid-gamma-aminobutyric acid system otherwise known as GABA. GABA is necessary for proper synaptic transmission in the CNS. Vitamin B₆ (pyridoxine) is vital to the production of GABA. If your B₆ is decreased then your GABA is decreased. INH decreases brain GABA levels by inhibiting the activity of pyridoxal-5-phosphate (necessary to metabolize GABA), and also by depleting the body's store of B₆. As little as 15 mg/kg of INH can lower the seizure threshold and 35-40 mg/kg produces spontaneous seizures in man.

The *metabolic acidosis* that occurs in INH toxicity is unique in that it is a *lactic acidosis*. Metabolic acidosis usually results from an accumulation of acid (other than carbonic) in the extracellular fluid or from a loss of bicarbonate in the extracellular fluid. Metabolic acidosis can be divided into two great groups; those with and without an *anion gap* (Is this really necessary? You can skip this part if you want to and resume reading in the section on treatment). Simply stated, the anion gap is calculated by adding together the extracellular concentrations of sodium and potassium and subtracting the chloride and bicarbonate concentrations. The normal range is 8-16 mEq/l with a mean of 12 mEq/l $[(Na + K) - (Cl + HCO_3)] = 12 \pm 2$ mEq/l]. If the patient has a metabolic acidosis with an increased anion gap (> 12 mEq/l) then you can assume that there has been an accumulation of an acid other than carbonic, such as in salicylate intoxication, methanol or ethylene glycol poisoning, uremic acidosis, diabetic ketoacidosis and *lactic acidosis*. In lactic acidosis the serum lactate level exceeds the normal of 9-16 mEq/l. If your patient has a lactic acidosis and you suspect a poison remember that the drugs in overdose that will cause this problem are such drugs as INH, ethanol and phenformin, etc. INH probably blocks the conversion of lactate to pyruvate but probably a major cause of lactic acidosis in INH toxicity occurs secondary to the repetitive seizures. (This is an issue still being debated, i.e., what is the major cause of the lactic acidosis in INH overdose?). As long as INH levels are not readily available you can determine if a patient with an alleged overdose has a metabolic acidosis. If the patient also has an increased anion gap you should obtain a serum lactate. If the serum lactate is elevated and you have a patient with a lactic acidosis, then that narrows the overdose possibilities to such toxins as phenformin (an oral hypoglycemic agent which is no longer commercially available in the U.S.), carbon monoxide, cyanide, ethanol, methanol and INH (there are others that will produce this state as well). Knowing the patient has a lactic acidosis and obtaining a good history of what drugs the patient had access to should make the diagnosis in many cases.

The laboratory investigation of this overdose at minimum consists of arterial blood gas determination, serum lactate levels, electrolytes (mild hypokalemia is not uncommon), blood glucose (hyperglycemia can occur), CBC (leukocytosis is a frequent visitor), urine analysis (glycosuria and ketonuria may be present suggesting diabetic ketoacidosis). Most hospital labs do not perform serum INH levels but for rapid qualitative detection of INH and its

metabolites the urine may be tested with a commercially available reagent-impregnated paper strip. If your hospital has the facilities the urine can be tested for the presence of an increased urinary excretion of pyridoxine. Some patients with INH overdose have a transient increase in the SGOT but this is not a constant finding. An EEG might be helpful. It is a good idea to measure the BUN and serum creatinine as renal function might be compromised.

By digesting all of the data thus far presented the treatment should be quite predictable although there are arguments, of course, concerning the best way to treat such a patient. Everyone would agree that the first step should be to make sure that you attempt to stabilize abnormal vital signs. I am sure that you are going to want to stop the seizures. The drug of choice is, you guessed it, *pyridoxine hydrochloride*. The purpose of giving pyridoxine is of course to increase the formation of the active coenzyme pyridoxal phosphate which is specifically inhibited by INH. The optimal dose of this antagonist should be at least equal to the maximum amount of INH allegedly ingested. The pyridoxine hydrochloride is mixed as a 5 or 10% solution with water and administered IV. If the patient allegedly swallowed 1 gram of INH you would give 1 gram of pyridoxine. Give the pyridoxine over a 5 minute period. You can repeat this dose at 5-20 minute intervals, if needed, in a comatose or convulsing patient. If you don't know the ingested dose start with 5 grams of pyridoxine. Many authorities believe that correcting the seizures corrects the lactic acidosis and they do not give sodium bicarbonate; others believe you need to correct the acidosis with sodium bicarbonate. Another variation of therapy concerns the use of diazepam. Some clinicians use this drug initially in an effort to stop the seizures; others would only use the drug if pyridoxine failed. Apparently diazepam increases GABA in the brain and also acts synergistically with pyridoxine. Once the life-threatening events are under control cautious gastric emptying should be performed as should the administration of activated charcoal and a saline cathartic. If all else fails, remember that INH has a small volume of distribution (< 1 l/kg) and very little protein binding and thus is a very good candidate for dialysis. Fortunately a patient with isoniazid overdose usually does not require this extracorporeal modality, i.e., the drug has a short life and pyridoxine is an efficient antidote.

I don't know about your classical tastes, but my two favorite operas are Puccini's *La Boheme* and Verdi's *La Traviata*. In both of these wonderful works, written in the 19th Century, the heroines die in the last act of what apparently is "consumption." In spite of their pulmonary compromise and obvious physical weakness, both Mimi (*La Boheme*) and Violetta (*La Traviata*) are able to bring tears to the eyes of the audience by singing beautiful arias at decibel levels that could shatter wine glasses. What would these composers do today? Would the female protagonists have to die from less dramatic late 20th Century diseases other than tuberculosis? Please spare me from operas where the heroine and main love interest dies from Legionnaires' disease, or perish forbid, AIDS!!

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Learning Without Words

Francis A. Neelon, M.D.

ONE year ago, when the first number of this *Journal* edited by Eugene A. Stead, Jr. appeared, he introduced a section that he called "*Learning Without Work*." Its purpose was to provide a means of communicating in brief, almost telegraphic form, those lessons that doctors learn every day from their patients. Practitioners are familiar with the phenomenon — they tell their colleagues about the exciting or novel or dramatic findings that come their way as they care for their patients. Dr. Stead hoped that those individuals who felt they had learned something new (or relearned something old) would be moved to communicate that lesson to the readers of the *Journal*. Indeed, I think it is clear from a year's experience that "*Learning Without Work*" has been a useful addition and has admirably succeeded in providing an otherwise unavailable vehicle for a kind of professional communication that "just comes naturally" to doctors.

Nevertheless, some actual or potential contributors seem uncertain about what topics are suitable or about what form their report should take. I believe that a touchstone is the following: Any time you say, aloud or to yourself, "What an interesting case" or "What a classic example of . . ." or "You should take a look at the patient in Room X" or "It's been a long time since I saw such a really nice demonstration of . . .," you have the germ of a contribution.

We are not looking for first (or second or seventy-ninth) cases of rare conditions or for exhaustive reviews of the literature with hundreds of references. Rather, we are seeking clear, concise descriptions of the learning that has come from experience. Case descriptions are helpful but they should not be presented in the stodgy or abstruse style favored by most medical journals, where the reader has to already be an expert in the field to comprehend what was

done to the patient and why. We encourage authors to intersperse their case reports with editorial comments about how they approached the diagnostic and therapeutic process and about what they were thinking at critical junctures in the development of the case. This is the narrative style that doctors use when they talk to their colleagues in hospital corridors and we believe it is appropriate for "*Learning Without Work*." Case reports should be based on real events (that is, not "invented" for illustrative purposes), but irrelevant details ("The VDRL was negative," etc.) should be omitted. Normal ranges for diagnostic tests should be given in the text. Throughout, the author must make the case report convey to the reader those lessons that the patient taught the doctor and that generated the desire to write in the first place.

The case report will usually be followed by a succinct summary of what the author learned and a few salient references. Of course, some topics may not derive from case experiences. In such instances we will be happy to consider other forms of brief reports, usually arising from the author's experience with and thinking about some aspect of practical reality and taking the general form of "What I know now that I did not know before."

One final point. As the Chinese knew, but many of our contributors forget, one picture is worth 10^x words! If you see something and want to write about it — take a photograph; draw a diagram; make a table! These visual aids convey information much more directly and concretely than any verbal message. They form a mental hook that grabs the reader's attention, and their impression is lasting. The reports by Li and by Pritchett elsewhere in this issue illustrate my point. Li's X-rays and Pritchett's diagram breathe life into their reports; without the visual impact, we'd be hard pressed to share the authors' sense of wonderment. Li and Pritchett have done us double service — by teaching us something we should know and by demonstrating the value of "*Learning Without Words*."

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Words of Wisdom from John Graham

John B. Graham, M.D.

I. Laws of Administration

The personal qualities of an administrator have an important effect on the outcome of events. The careful administrator leaves nothing to chance. He must be a successful "politician," in the non-invidious sense, always seeking common ground between contending parties and views. Many of his problems are ambiguous and he must make decisions that affect the lives and careers of others.¹ It is the rare person who can be a successful administrator for very long without alienating so many people that he becomes ineffective. If the admonitions below are carefully followed, the inevitable day of ineffectiveness will be postponed for many years.

1. Make decisions promptly but not precipitately after considering at least briefly the secondary and tertiary effects of each.

2. Reverse as few decisions as possible. Frequent reversals cause others to suspect that you are either (a) stupid, (b) indecisive, or (c) dishonest. The good administrator tries to be predictable and always keep his promises (and threats).

3. Cultivate "gravitas"² and "inscrutability."³

4. Be certain that paper work is accurate and delivered on time. Plan ahead to avoid the turbulence associated with unalterable deadlines. Try to conform to John Randolph's description of Martin Van Buren, the perfect administrator: "He rowed with muffled oars."

5. Treat your *subordinates* with scrupulous fairness and courtesy. Bend over backward to demonstrate your interest in their welfare. Defend them against outsiders, and never blame them for your errors. If you mistreat them, they will damage you later if only by sabotage.

6. Remember that your *peers and superiors* are highly intelligent, insecure, and slightly paranoid. Regard each one as a bomb on a hair-trigger which may explode at the most unintended slight. Peers and superiors are particularly

concerned about their images and territories. Never threaten anyone's image or territory, except deliberately. Always make a careful analysis of benefits and costs before doing so.

7. Always be accessible and keep your appointments scrupulously. Not to be or do so suggests to others that you do not value them highly. (See paranoia above.)

8. *Always* have a witness present if you wish to be certain that a decision will withstand legal testing at a later time.

9. *Never* have a witness present if you may wish to issue a denial later.

10. Be careful about what you put in writing. Never say more than the absolute minimum.⁴

II. The Acquisition, Enhancement and Erosion of the Capital Asset, Good Will

Good will should be treated as a capital asset. It has peculiar properties, however. Acquisition occurs only once; enhancement is slow and difficult; and erosion may be very rapid. It differs from other capital assets in not being subject to the laws of interest; it does not compound while lying unused. In short, good will seems to be a unidirectional asset, only eroding with time.

When one joins an organization, he acquires a quantum of good will. (It is said of him that he is "in the honeymoon period" initially.) If carefully husbanded, his quantum may last for an entire career. Usually, however, it has been frittered away long before retirement. Rates of erosion vary from the almost zero rate of the careful, low-profiled person who never creates waves and does only favors for others, to the rapid rate characteristic of those who live from crisis-to-crisis at the expense of the nervous systems of their peers and subordinates.

Enhancement of good will is possible only for those who are in a position to do favors for others. The amount of enhancement is never great, however. The recipients of favors quickly forget that they have received favors and usually feel that there have not been any favors *lately*.

When representing clients, lawyers seem to be able to act as adversaries without breaking friendships. (Lawyers have been observed, however, to acquire permanent enemies when representing *themselves* in adversarial situations.) The young and naive have inferred from the courtroom experience of lawyers that they can practice adversarial tactics with impunity. Nothing could be further from the truth. The information networks of institutions are numerous and complex and institutional memory is cumulative. A price is paid in loss of good will with each adversarial encounter, whoever wins. Thus tactics of the type some-

¹ Devote your energies to selecting superior personnel. It is more rewarding and less traumatic than getting rid of inferior ones.

² Most people lack a sense of humor, especially when their own interests are concerned. If you conceal yours, they will find it easier to relate to you. Concealment also throws off persons having a sense of humor who will not know quite how to deal with you. There is a theory at the Harvard Business School that having hemorrhoids is advantageous for an administrator. The slightly pained expression that they give him makes interviewees think that he is listening attentively, and the pain provides him with insight into the problems of ordinary people.

³ Locate a confidant for blowing off at intervals. Never explode publicly except deliberately, for its effect on others.

⁴ This law does not apply to entrepreneurs. "Hype" is their natural mode of expression.

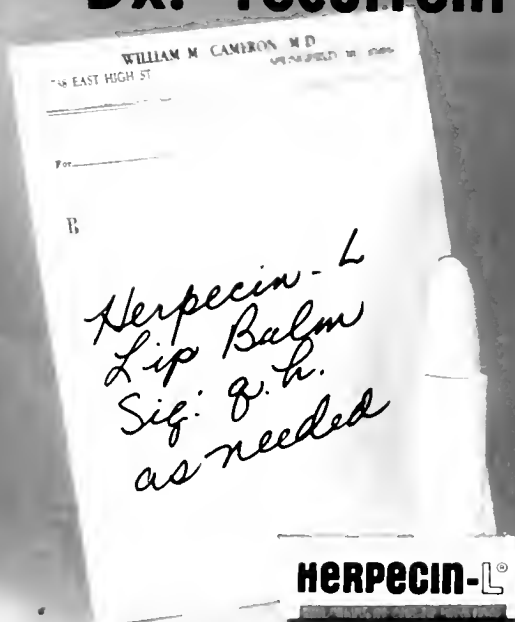
times referred to in the U.S. as the "northeastern style" can rapidly erode a stock of good will. The practitioner of adversarial tactics may suddenly discover that he lacks influential friends when he needs them most. This, of course, is the prudential basis for husbanding good will.

Good will may erode to zero, even become a negative quantity. When it becomes negative, it is referred to as "hostility." Once an individual becomes the general object of hostility, he becomes ineffective and must be either (1) put out to pasture, (2) discharged or (3) transferred. If such a person is to regain good will as a significant positive asset, he must change institutions, preferably moving to one sufficiently far removed that his reputation is not known. Such individuals are generally poor prospective

employees, however, because their characters are usually fixed, and they will probably get into the same difficulties in a new institution.

There is an exception to all these rules. They do not apply to *STARS*! A STAR is universally respected, and respect may be a fully adequate substitute for good will. (A true STAR can get away with being an absolute bastard.) There is a tragic exception here, however. This is the case of the individual who thinks that he is a STAR but whose luminosity is less than he thinks. He may erode his good will asset under this mistaken impression and discover too late that it has been exhausted. Then he is in the predicament of a universally-recognized son-of-a-bitch.

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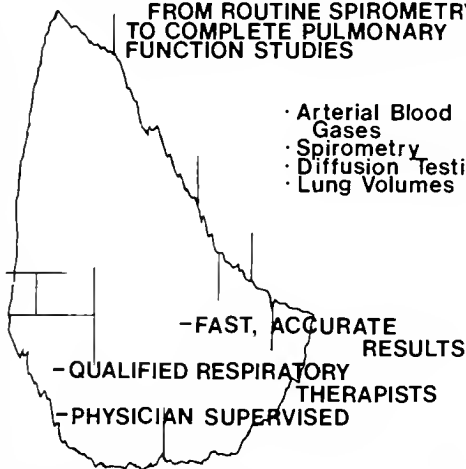
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BRIEF SUMMARY

PROCARDIA® (nifedipine) CAPSULES

For Oral Use

INDICATIONS AND USAGE 1. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation; 2) angina or coronary artery spasm provoked by ergonovine; or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

2. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina. Effort-associated angina without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long term safety in those patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: **Excessive Hypotension:** Although in most patients the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, or in other surgical procedures, or with other narcotic anesthetics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: **General Hypotension:** Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug Interactions: Beta-adrenergic blocking agents. (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the effects of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Carcinogenesis, mutagenesis, impairment of fertility: When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose.

Pregnancy: Category C. Please see full prescribing information with reference to teratogenicity in rats, embryofetotoxicity in mice and rabbits and abnormalities in monkeys.

ADVERSE REACTIONS: The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients; transient hypotension in about 5%; palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, diarrhea, constipation, inflammation, joint stiffness, shakiness, sleep disturbance, blurred vision, difficulty in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, and sexual difficulties. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

Laboratory Tests: Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms. Cholestasis, possibly due to PROCARDIA therapy, has been reported twice in the extensive world literature.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA CAPSULE contains 10 mg of nifedipine. PROCARDIA CAPSULES are supplied in bottles of 100 (NDC 0069-2600 661), 300 (NDC 0069-2600 721) and unit dose (10x10) (NDC 0069-2600 41). The capsules should be protected from light and moisture and stored at controlled room temperature 59 to 77 F (15 to 25 C) in the manufacturer's original container.

More detailed professional information available on request.

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Quotes from an unsolicited letter received by Pfizer from an angina patient. While this patient's experience is representative of many unsolicited comments received, not all patients will respond to PROCARDIA nor will they all respond to the same degree.

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Please see PROCARDIA brief summary on adjoining page

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When Is a Stomach Bubble Not a Stomach Bubble?

Answer: When It Is an Abscess!

James T. C. Li, M.D., Ph.D.

IN medicine, as in life, things are not always what they appear to be. In this report, an innocuous-appearing stomach bubble turned out to be part of a fatal illness. There were radiographic clues that might have tipped us off to the presence of a left subphrenic abscess.

This 66-year-old black man, who had lost 60 pounds in the last six months, had had cramping periumbilical pain for four weeks with mild post-prandial nausea and vomiting but no hematemesis. One day prior to admission, the patient developed fever, chills, and generalized weakness. He had a history of well controlled Type II diabetes mellitus and mild hypertension. There was no history of abdominal surgery.

The patient was in no acute distress. His temperature was 38.9 degrees Celsius, his pulse was 104/min and respirations 20/min. Pertinent findings on physical examination included bibasilar rales and a vague fullness to palpation in

the left upper quadrant. There was occult blood in his stool.

The hematocrit reading was 30% and white blood cell count was 19,800 per mm³ with a left shift. The chest X-ray (figure 1, left panel) revealed small bilateral pleural effusions and an elevated left hemidiaphragm. Initially, neither the Emergency Room physicians nor the radiology resident commented on the stomach bubble.

A few hours later, the radiology attending noted that the featureless borders of the air-fluid level extended more laterally than usual. A limited upper GI series using water soluble contrast (figure 1, right panel) showed a 10 cm air-fluid level in the left upper quadrant distinct from the normal stomach.

At laparotomy, a nodular mass in the splenic flexure was found and biopsied. Above this mass was a larger fluctuant mass from which 800 ml of pus was drained. The biopsy showed poorly differentiated adenocarcinoma of colon. There were no immediate postoperative complications but the patient suffered a cardiac arrest on the third hospital day and died on the ninth hospital day.

From the Department of Medicine, Duke University Medical Center, Durham 27710.

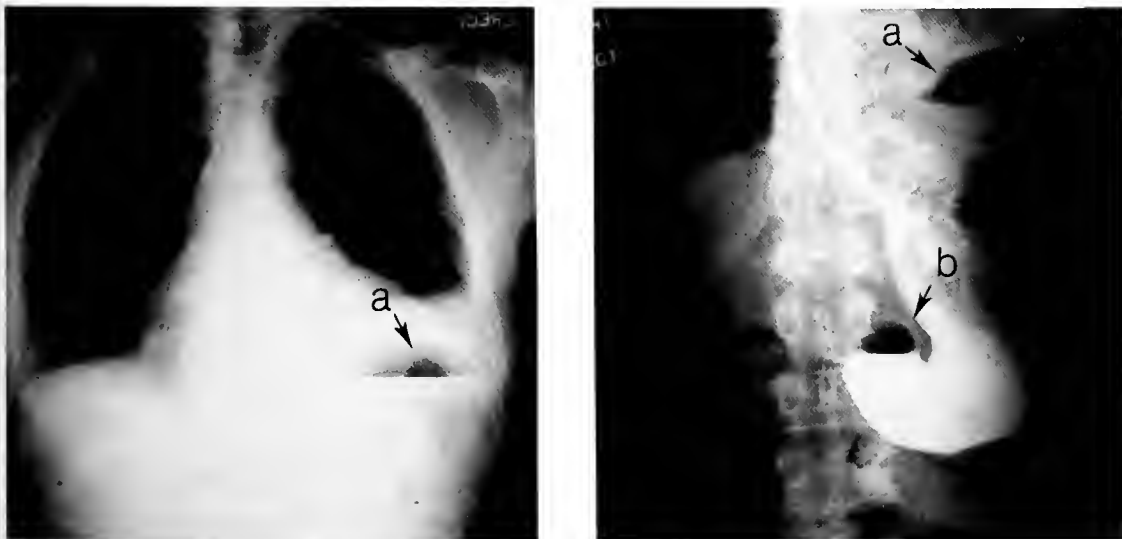


Figure 1. Left panel shows bilateral pleural effusions, elevated left hemidiaphragm and a normal appearing stomach bubble (a). Right panel shows left subphrenic abscess (b) distinct from stomach.

Discussion

The upper abdominal abscess is a life-threatening infection with a mortality approaching 30%.¹ In one study, 78% of cases of abdominal abscess occurred following abdominal surgery; the remainder were associated with perforated viscus.¹ Radiologic diagnosis is very important in these cases because so many of them are non-specific on presentation. In our patient, the abscess was not noted on initial examination of the plain films even though there were several radiologic clues that suggested the presence of a left subphrenic abscess.

Well-known radiographic features associated with subphrenic abscess include unilateral or bilateral pleural effusions, elevated hemidiaphragm and decreased diaphragmatic movement.² The abscess itself may appear as a soft-tissue mass or, characteristically, as an air-fluid level. Differentiation of normal stomach or bowel from an intra-abdominal abscess may be difficult. In a recent review of 58 patients with upper abdominal abscess exhibiting extraluminal gas or soft-tissue mass on plain film, 16 were initially missed, including one case simulating a stomach bubble.¹ Abscess in the left upper quadrant is more difficult to identify because of the presence of the stomach and colon, as illustrated in our case. An air-fluid level that extends laterally to the chest wall or medially across the midline³ is likely to represent abscess rather than stomach. The absence of rugal folds in a left upper quadrant air-fluid level likewise suggests abscess. Finally, if old films are available, the persistence of an unchanging "stomach bub-

ble" should suggest the possibility of subphrenic abscess.

Once the suspicion of abscess exists, further investigation is warranted. The increased penetration of an abdominal film may reveal a double gas-fluid level or a soft-tissue mass. A repeat plain film following nasogastric suction or the introduction of air or saline into the stomach may identify extraluminal gas distinct from stomach. The simple and underutilized upper GI series is an extremely effective method for identifying abdominal abscesses. This study may reveal extravasation of contrast, distorted bowel anatomy or extraluminal gas. Finally, abdominal CT scan and ultrasound are both highly accurate in demonstrating abdominal abscess. The CT scan not only is sensitive (96%) and specific (87%),⁴ but also can provide detailed preoperative anatomy.

The key to the diagnosis in our case, however, was a suspicious and skeptical mind, not multiple radiographs. Clues that may be present on a plain film cannot be seen unless looked for with a critical eye.

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When Is a Drug Side Effect a Therapeutic Effect?

Edward L. C. Pritchett, M.D.

THE calcium channel blocking drugs like verapamil form an important new therapeutic class. These agents exert their therapeutic effects on supraventricular tachycardia by slowing atrioventricular nodal conduction and exert their therapeutic effect on angina by dilating arteries. Intravenous verapamil is extremely potent in terminating paroxysmal atrial tachycardia (figure 1) and in slowing the ventricular rate in atrial fibrillation and atrial flutter.

What, then, would we expect to see on the electrocardiogram of a patient taking oral verapamil who was in normal sinus rhythm rather than in a supraventricular tachycardia?

Slowing nodal conduction is manifested on the scalar electrocardiogram as a prolongation of the PR interval while heart rate, QRS morphology, ST segment, and T waves remain unchanged. We would, therefore, expect to see PR interval prolongation in a patient taking oral verapamil; it is an *expected* drug effect. PR interval prolongation is a measurable marker of drug activity. It provides reassurance that the patient is taking his drug and that the drug is being absorbed. Importantly, prolongation of the PR interval is not a criterion for reducing the dose or discontinuing the use of verapamil. In extremely rare cases, a patient may develop Mobitz type 1 2° atrioventricular block (Wenckebach); only then does the drug effect become a true side effect and a reason to reduce drug dose.

From the Department of Medicine, Duke University Medical Center, Durham 27710.

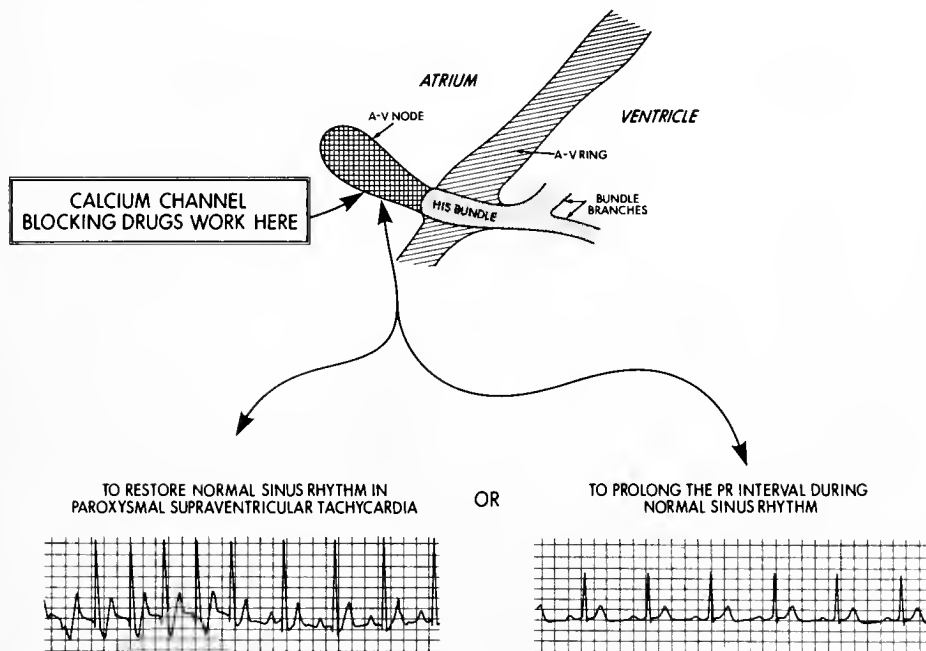


Figure 1. Atrioventricular nodal conduction is markedly slowed by verapamil. This effect leads to termination of paroxysmal atrial tachycardia (left electrocardiogram) and to prolongation of the PR interval during sinus rhythm (right electrocardiogram).

Roche salutes
the history of North Carolina medicine

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A modern-day version of the country doctor on horseback, Dr. Gaine Cannon covered his scattered practice around the Blue Ridge Mountain country near Balsam Grove, North Carolina, in a four-wheel-drive Jeep wagon.¹

On an average working day, Dr. Cannon rose at sunup to see patients at his converted-farmhouse clinic before setting out to make his usual 15 to 20 house calls around the countryside. Generally, after treating his primary patient, he saw each member of the family as well—his personal effort at preventive medicine.

Multiple services

With the nearest hospital some 60 miles away and no pharmacy closer than an hour-and-a-half drive, Dr. Cannon filled his own prescriptions, delivered babies

and treated many patients at a centrally located general store with the most modern techniques and medications. After a day on the road—usually within a 50-mile radius—Dr. Cannon's office hours would begin at 5:30 p.m. and stretch on until the last patient was attended to. His record-keeping sessions routinely filled the hour before midnight—rounding off Dr. Cannon's 18-hour day.

At all hours

But emergencies often interrupted his sleep. Dr. Cannon claimed his real office hours were 24 hours a day, and his patients revered him for it.

Dr. Cannon died in 1966 at the age of 68. He will be long remembered—most especially by the more than 5000 North Carolinians he helped bring into the world, some of them at the side of a rutted country road.

Reference. 1. Doctor in the backwoods, in Lee RV, Eimert S et al: *The Physician*. New York, Life Science Library, Time Inc., 1967, pp 38-50



ROCHE

When the history reveals mixed depression and anxiety...

For the estimated 70 percent of nonpsychiatric depressed patients who are also anxious,¹ Limbitrol provides both amitriptyline, specific for symptoms of depression, and the effects of Librium® (chlordiazepoxide HCl/Roche), the tested and dependable anxiolytic. Limbitrol is, therefore, a better choice for these patients than dual agents that contain a phenothiazine, a class of antipsychotic drugs which has been associated with tardive dyskinesia.

62% of Overall Improvement...Within the First Week

Limbitrol also has a rapid onset of action which may lead to greater patient compliance. In a multicenter study, patients taking Limbitrol experienced 62% of their overall improvement within the first week of therapy.²

In another multicenter study,³ the following symptoms associated with anxious depression were significantly reduced during the first two weeks of therapy:

- ☐ Headache—79%
- ☐ Early insomnia—91%
- Middle insomnia—87%
- Late insomnia—89%
- ☐ Gastrointestinal upset—73%

In two multicenter studies, only 1.9% of Limbitrol patients experienced cardiovascular side effects.³

Patients should be cautioned about the combined effects with alcohol or other CNS depressants and about activities requiring complete mental alertness such as operating machinery or driving a car.

References: 1. Rickels K: Drug treatment of anxiety, in *Psychopharmacology in the Practice of Medicine*, edited by Jarvik ME, New York, Appleton-Century-Crofts, 1977, p 316 2. Feighner JP et al: *Psychopharmacology* 61: 217-229, Mar 1979 3. Data on file, Hoffmann-La Roche Inc., Nutley, NJ

In moderate depression and anxiety

Limbitrol®

Tablets 5-12.5 each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)

Tablets 10-25 each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt)

Please see summary of product information on following page.

LIMBITROL® Tablets (N) Tranquillizer-Anidepressant

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of moderate to severe depression associated with moderate to severe anxiety.

Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use. Then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction.

Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

Usage in Pregnancy: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage. Withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline, symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs.

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. IV administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly.

Limbitrol 10-25, initial dosage of three or four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol 5-12.5, initial dosage of three or four tablets daily in divided doses, for patients who do not tolerate higher doses.

How Supplied: White, film-coated tablets, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt) and blue, film-coated tablets, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500, Tel-E-Dose® packages of 100, Prescription Paks of 50.

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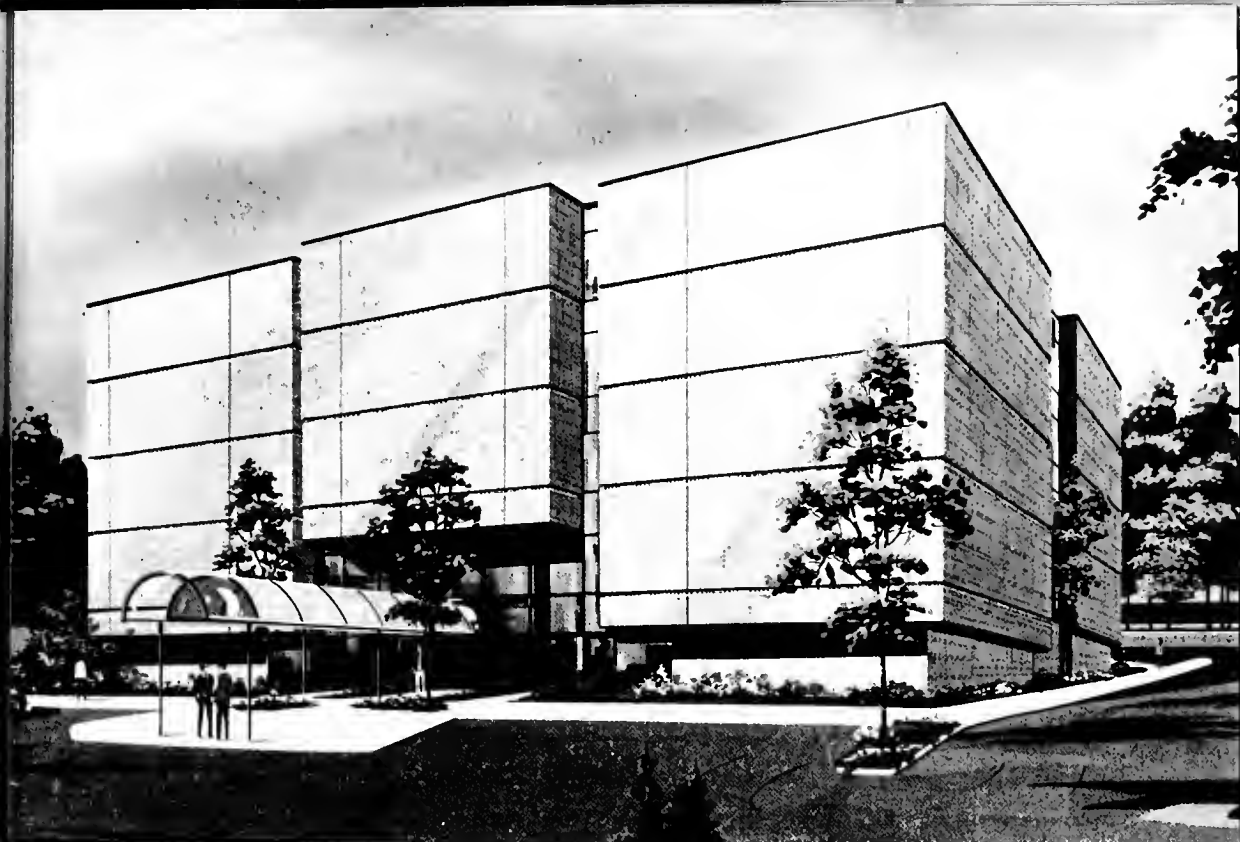
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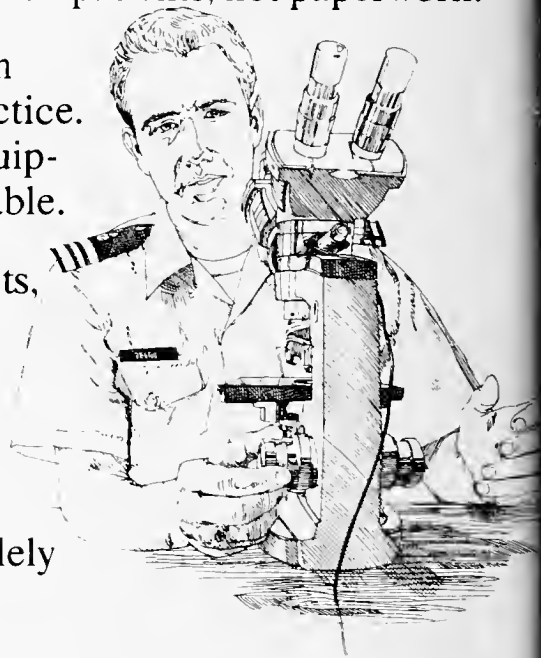
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- ☐ CORZIDE combines the advantages of CORGARD® (nadolol) — the highly effective once-a-day beta-blocker — and a classic once-a-day thiazide
- ☐ CORZIDE reduces blood pressure, as demonstrated in clinical trials

for a low incidence of side effects†

- ☐ CORZIDE was well tolerated in 102 patients evaluated for adverse reactions
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*This fixed combination drug is not indicated for initial therapy of hypertension. It may be appropriate if the fixed combination represents the dosage as titrated to the individual patient's needs.

†Please see brief summary of prescribing information on the last page of this advertisement for a discussion of CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS and WARNINGS, including avoidance of abrupt withdrawal.

ONCE-A-DAY
CORZIDE®
Nadolol-Bendroflumethiazide Tablets

**An important advance in Step-2
antihypertensive therapy**

For brief summary please see next page.

ONCE-A-DAY

CORZIDE

Nadolol-Bendroflumethiazide Tablets



An important advance in Step-2 antihypertensive therapy

CORZIDE, 40/5

CORZIDE, 80/5

Nadolol-Bendroflumethiazide Tablets

DESCRIPTION: CORZIDE (Nadolol-Bendroflumethiazide Tablets) for oral administration contains two antihypertensive agents: CORGARD® (nadolol), a selective beta-adrenergic blocking agent, and NATUPELIN® (bendroflumethiazide), a thiazide diuretic-antihypertensive. Formulations: 40 mg and 80 mg nadolol per tablet combined with 5 mg bendroflumethiazide.

CONTRAINDICATIONS: 1 — Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS). Bendroflumethiazide 2 — Anuria, and in those with previous hypersensitivity to bendroflumethiazide or other sulfonamide-derived drugs.

WARNINGS: Nadolol 1 — **Cardiac Failure** — Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, digitalis and/or diuretics, and closely observe response or discontinue nadolol (gradually, if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy, exacerbation of angina, and in some cases, myocardial infarction have occurred after abrupt discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstatement nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of beta₂ receptors. **Major Surgery** — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase the risks of general anesthesia and surgical procedures, resulting in prolonged hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents. **Diabetes and Hypoglycemia** — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hypoglycemia; therefore, it may be necessary to adjust dose of anti-diabetic drugs. **Thyrotoxicosis** — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

Bendroflumethiazide — Use with caution in severe renal disease. In patients with renal disease, azotemia may be precipitated. With impaired renal function, effects of the drug may be cumulative. Use with caution in impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

PRECAUTIONS: General — Nadolol 1 — Use with caution in patients with impaired hepatic or renal function (see DOSAGE AND ADMINISTRATION).

Bendroflumethiazide — At appropriate intervals, perform serum electrolytes determination to detect possible electrolyte imbalance warning signs of which are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and GI disturbances such as nausea and vomiting. Observe patients for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Drugs such as digitalis may influence serum electrolytes. Hypokalemia may develop, especially with brisk diuresis, in presence of severe cirrhosis. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Response of the heart to toxic effects of digitalis can be exaggerated with hypokalemia. Use potassium supplements such as high potassium foods to avoid or treat hypokalemia. Any chloride deficit is generally mild and usually does not require special therapy except under extraordinary circumstances (as in liver or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than salt administration except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain thiazide-treated patients. Latent diabetes mellitus may become manifest during thiazide therapy. Antihypertensive effects of bendroflumethiazide may be enhanced in the post-sympathectomy patient.

Careful reappraisal of therapy and consideration given to withholding or stopping appropriate therapy is necessary if rising nonprotein nitrogen or BUN indicative of progressive renal impairment occurs. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Thiazides decrease calcium excretion. Pathologic changes in parathyroid gland with hypercalcemia and hypophosphatemia have been occasionally observed with prolonged therapy. Common complications of hyperparathyroidism have not been seen.

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at the first sign or symptom of impending failure. Advise patients of proper course if dose inadvertently missed.

Laboratory Tests — Regularly monitor serum and urine electrolyte levels (see WARNINGS, Bendroflumethiazide, and PRECAUTIONS, General, Bendroflumethiazide).

Drug Interactions — Nadolol 1 — When administered concurrently the following drugs may interact with beta-adrenergic blocking agents: **Anesthetics, general** — exaggeration of anesthetic-induced hypotension (see WARNINGS, Nadolol, Major Surgery). **Anti-diabetic drugs (oral agents and insulin)** — hypoglycemia or hyperglycemia, adjust anti-diabetic dosage accordingly (see WARNINGS, Nadolol, Diabetes and Hypoglycemia). **Catecholamine-depleting drugs (e.g., reserpine)** — additive effect, monitor closely for evidence of hypotension and/or excessive bradycardia.

Bendroflumethiazide — When administered concurrently the following drugs may interact with thiazide diuretics: **Alcohol, barbiturates, or narcotics** — may potentiate orthostatic hypotension. **Antidiabetic drugs (oral agents and insulin)** — thiazide-induced hyperglycemia may require adjustment of anti-diabetic drug dosage. **Other antihypertensive drugs** — additive or potentiated effect. **Corticosteroids, ACTH** — intensified electrolyte depletion, particularly hypokalemia. **Angiotensin or peripheral adrenergic blocking drugs** — potentiated effect. **Prenesthetic and anesthetic agents** — effects may be potentiated, adjust dosage accordingly. **Pressor amines (e.g., norepinephrine)** — possible decrease response but not sufficient to preclude their use. **Skeletal muscle relaxants, nondopaminergic (e.g., tubocurarine)** — possible increased response.

Drug/Laboratory Test Interactions — Discontinue thiazides before tests for parathyroid function (see PRECAUTIONS, General, Bendroflumethiazide).

Carcinogenesis, Mutagenesis, Impairment of Fertility — Nadolol — In 1 to 2 years oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions. **Bendroflumethiazide** — Long-term studies in animals have not been performed.

Pregnancy — **Teratogenic Effects** — Nadolol — Category C. In animal reproduction studies with nadolol, evidence of embryo and/or fetotoxicity was found in rabbits, but not in rats or hamsters, at doses 5 to 10 times greater (on a mg/kg basis) than the maximum indicated human dose, no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women, therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. **Bendroflumethiazide** — Category C. Animal reproduction studies have not been conducted. This drug's effect on the fetus when administered to a pregnant woman or its effect on reproductive capacity is not known. Bendroflumethiazide should be given to a pregnant woman only if clearly needed. **Nonteratogenic Effects** — Since thiazides cross the placental barrier and appear in cord blood, weight antepartum benefit of the drug in pregnant women against possible hazards to the fetus, these hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other reactions which have occurred in adults.

Nursing Mothers — Both nadolol and bendroflumethiazide are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants either discontinue nursing or discontinue the drug, taking into account the importance of CORZIDE (Nadolol-Bendroflumethiazide Tablets) to the mother.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Nadolol — Most adverse effects have been mild and transient and have rarely required nadolol withdrawal. **Cardiovascular** — Bradycardia with heart rate of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of heart block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients, paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients.

Respiratory — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash, pruritus, headache, dry mouth, eyes, or skin, impotence or decreased libido, facial swelling, weight gain, slurred speech, cough, nasal stuffiness, sweating, tinnitus, blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with procainol has not been reported with nadolol. The following adverse reactions may also occur. **Central Nervous System** — reversible mental depression progressing to cataplexy, visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat, laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia, Peyronie's disease; erythematous rash, arterial insufficiency.

Bendroflumethiazide **Gastrointestinal System** — anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis. **Central Nervous System** — dizziness, vertigo, paresthesia, headache, xanthopsia. **Hematologic** — leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia. **Dermatologic-Hypersensitivity** — purpura, photosensitivity, rash, urticaria, necrotizing angitis (vasculitis, cutaneous vasculitis). **Cardiovascular** — orthostatic hypotension may occur. **Other** — hyperglycemia, glycosuria, occasional metabolic acidosis in diabetics, hyperuricemia, allergic glomerulonephritis, muscle spasm, weakness, restlessness. Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

OVERDOSE: Nadolol may cause excessive bradycardia, cardiac failure, hypotension, or bronchospasm if overdosed. Overdose of thiazides may cause lethargy, which may progress to coma within a few hours, with minimal depression of respiration and cardiovascular function and without evidence of serum electrolyte changes or dehydration. Gastrointestinal irritation and hypernatremia may occur. Transitory increase in BUN and serum electrolyte changes may occur, especially in patients with renal impairment.

Treatment — Nadolol can be removed from the general circulation by hemodialysis. In determining duration of correction therapy, take note of the long duration of the effect of nadolol in addition to gastric lavage, employ the following measures, as appropriate: **Excessive Bradycardia** — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously. **Cardiac Failure** — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.) **Bronchospasm** — Administer a beta-stimulating agent or a theophylline derivative. **Support or Coma** — Supportive therapy as warranted. **Gastrointestinal Effects** — Symptomatic treatment as needed. **BUN and/or Serum Electrolyte Abnormalities** — Institute supportive measures as required to maintain hydration, electrolyte balance, respiration, and cardiovascular and renal function.

DOSAGE AND ADMINISTRATION: DOSAGE MUST BE INDIVIDUALIZED. Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

Consult package insert before prescribing CORZIDE (Nadolol-Bendroflumethiazide Tablets).

HOW SUPPLIED: Available as scored tablets containing 40 mg nadolol combined with 5 mg bendroflumethiazide and 80 mg nadolol combined with 5 mg bendroflumethiazide in bottles of 100.

Bulletin Board

Continuing Medical Education

Please note: 1. The Continuing Medical Education Programs at Bowman Gray, Duke, East Carolina and UNC Schools of Medicine, Dorothea Dix, and Burroughs Wellcome Company are accredited by the American Medical Association. Therefore CME programs sponsored or cosponsored by these schools automatically qualify for AMA Category I credit toward the AMA's Physician Recognition Award, and for North Carolina Medical Society Category A credit. Where AAFP credit has been obtained, this also is indicated.

IN STATE

May 10-11

Infectious Disease Update 1984
Place: Greensboro
Fee: \$75
Credit: 11 hours Category I AMA
Info: Fred Levick, Greensboro AHEC, 1200 North Elm Street, Greensboro 27401. 919/379-4025

May 10-12

North Carolina Chapter of the American College of Surgeons
Place: Boone
Info: Richard W. Furman, M.D., 702 State Farm Road, Boone 28607. 704/264-2340

May 16

Progress on Type 2 Diabetes
Place: Raleigh
Fee: None
Credit: 3 hours
Info: B. Neilson, UNC School of Medicine, 231 MacNider Bldg 202H, Chapel Hill 27514. 919/962-2118

May 17

Records and Other Necessities
Place: Asheville
Info: Wayne Parker. 919/828-9334

May 17-18

Social Behavior in Autism
Place: Chapel Hill
Fee: \$25 in-state; \$100 out-of-state
Credit: 12 hours
Info: B. Neilson, UNC School of Medicine, 231 MacNider Bldg 202H, Chapel Hill 27514. 919/962-2118

May 17-19

Floyd W. Denny Alumni Lecture Series
Place: Chapel Hill
Info: Gerald W. Fernald, M.D., Pediatrics, 509 Burnett-Womack Bldg, 229H, UNC School of Medicine, Chapel Hill 27514. 919/966-2085

May 18-20

Pathokinesiology of Cerebral Palsy
Place: Chapel Hill
Info: Darlene S. Slaton, Physical Therapy, C 221H, UNC School of Medicine, Chapel Hill 27514. 919/966-4708

May 24

Records and Other Necessities
Place: Shelby
Info: Wayne Parker. 919/828-9334

May 25-26

13th Annual Seminar: Gut and Lung Problems in Pediatrics
Place: Durham
Credit: 12 hours
Fee: \$60
Info: Alexander Spock, M.D., Box 2994 Duke University Medical Center, Durham 27710. 919/681-3364

May 25

Pediatrics Day
Place: Greenville
Credit: 7 hours
Fee: \$55
Info: Mary C. Valand, Box 7224 ECU School of Medicine, Greenville 27834. 919/758-5200

May 31-June 2

The Sea Level Invitational Conference on Geriatric Medicine
Place: Sea Level
Info: M. Valand, ECU School of Medicine, PO Box 7224, Greenville 27834. 919/758-5200, ext 208

May 31-June 2

Approaches to Ethical Decision Making
Place: Durham
Info: Nettie Wilburn, UNC-CH School of Nursing, Carrington Hall 214H, Chapel Hill 27514. 919/966-3638

June

Sports Medicine Seminar
Place: UNC
Info: B. F. LeVeau, Physical Therapy, Wing C-221H, Chapel Hill 27514. 919/966-5005

June 1-2

Neurology for the Primary Physician
Place: Chapel Hill
Fee: \$100
Credit: 11 hours
Info: B. Neilson, UNC School of Medicine, 231 MacNider Bldg 202H, Chapel Hill 27514. 919/962-2118.

June 5

Duke Tuesday
Place: Durham
Credit: 5 hours
Info: L. Mace, Urology, Duke U Med Center, Box 3707, Durham 27710. 919/684-2033

June 6-7

Fellows Symposium
Place: Chapel Hill
Info: John J. Frey, M.D., 231 MacNider Bldg 202H, Chapel Hill 27514.

June 17-22

Health Promotion — Wellness Institute
Place: Raleigh
Fee: \$250
Credit: 30 hours
Info: NC Health Promotion, Wake AHEC, 3000 New Bern Ave, Raleigh 27610. 919/755-8018

June 20

Suicide by Poisoning
Place: Sanford
Credit: 2 hours
Info: R. S. Cline, M.D., Central Carolina Hospital, 1135 Carthage St, Sanford 27330. 919/774-4100, ext 394

June 22-23

North Carolina Affiliate, American Heart Association,
35th Annual Meeting and Scientific Sessions
Place: Durham
Info: N.C. Heart Association, Chapel Hill 27514

July 9-14

26th Annual Postgraduate Course/Morehead Symposium
Place: Atlantic Beach
Credit: 25 hours
Info: C. Easterling, Duke U Medical Center, Box 3306, Durham 27710. 919/684-6485

July 18

Hospital Nutrition Update

Place: Sanford
Credit: 2 hours
Info: R. S. Cline, M.D., Central Carolina Hospital, 1135 Carthage St.
Sanford 27330. 919/774-4100, ext 394

July 30-August 3

Diagnostic Imaging
Place: Atlantic Beach
Fee: \$400; \$250 if in training and with letter from chairman
Credit: 26 hours
Info: J. D. Wright, Box 3808 Duke Hospital, Durham 27710. 919/681-2711

August 4

Geriatric Education Day
Place: Raleigh
Credit: 4 hours
Info: NCAFP 919/781-6457

August 7

Malpractice Awareness — STAT
Place: Greensboro
Info: Wayne Parker. 919/828-9334

August 14

Malpractice Awareness — STAT
Place: Charlotte
Info: Wayne Parker. 919/828-9334

August 15

Electrolytes/Arterial Blood Gases/Fluid Balance
Place: Sanford
Credit: 2 hours
Info: R. S. Cline, M.D., Central Carolina Hospital, 1135 Carthage St.
Sanford 27330. 919/774-4100, ext 394

August 21

Malpractice Awareness — STAT
Place: Goldsboro
Info: Wayne Parker. 919/828-9334

OUT OF STATE

May 7-9

Gold Coast Seminar: Medicine
Place: West Palm Beach, FL
Credit: AMA, AAFP
Info: Continuing Medical Education, Box 3306 Duke University
Medical Center, Durham 27710. 919/684-6485

May 10-12

Current Concepts of Clinical Infectious Diseases
Place: Hot Springs, VA
Fee: \$220, \$165, \$295
Credit: 13 1/2
Info: Gerald L. Mandell, M.D., Univ of Virginia, Charlottesville

May 18

A Seminar on Investigation of Sex Crimes
Place: Johnson City, Tenn.
Fee: \$40
Credit: 8 hours
Info: Sue Hutchinson, Office of CME. 615/928-6426, ext 204

May 18-19

Practical Dermatology for the Non-Dermatologist
Place: Williamsburg, VA
Fee: \$90
Credit: 7 hours
Info: B. Neilson, UNC School of Medicine, 231 MacNider Bldg
202H, Chapel Hill 27514. 919/962-2118

May 24-27

8th Annual Radiology Symposium
Place: Hilton Head, SC
Fee: \$350
Credit: 19 hours
Info: B. Neilson, UNC School of Medicine, 231 MacNider Bldg
202H, Chapel Hill 27514. 919/962-2118

May 30-June 2

AACA 1984 Spring Seminar in Anesthesiology
Place: Hilton Head, SC

Info: Amer Academy of Clinical Anesthesiologists, P.O. Box 11691,
Knoxville, TN 37939-1681. 615/588-6279

May 31-June 2

The Sea Level Invitational Conference on Geriatric Medicine
Place: Sea Level, GA
Info: Mary C. Valand, CME, ECU School of Medicine, Greenville
27834. 919/758-5200

June 4-8

Cornell University Diagnostic Radiology Update Emphasizing Advances
in Imaging and Interventional Procedures
Place: Bermuda
Credit: 100 hours
Fee: \$400, \$300
Info: Ann Wold, Gallagher/Wold, Inc., 420 Lexington Ave., New
York 10170. 212/986-1277.

June 18-July 1

The Cancer Patient: Surgical Treatment and Rehabilitation
Place: Cruise Benice, Yugoslavia, Greece, Turkey, Russia
Info: C. Easterling, Box 3306 Duke Hospital, Durham 27710. 919/
684-6485

June 27-30

Dermatology for Non-Dermatologists
Place: Myrtle Beach, SC
Credit: 15.5 hours Category 1 AMA
Fee: \$350
Info: Dermatology, Box 2987 Duke University Medical Center,
Durham 27710. 919/684-6728

July 2-7

Midsummer Family Practice Digest
Place: Myrtle Beach, SC
Credit: 30 hours
Info: NCAFP. 919/781-6476

July 26-28

6th Annual Pediatrics Primary Care Conference
Place: Virginia Beach, VA
Fee: \$275
Credit: 12 hours
Info: S. Rosner, Box 48 MCV Station, Richmond, VA 23298. 804/
786-0494

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Howard Edward Miller (ORS), 723 Edith Street, Burlington
27215

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David Alan Desrochers (R), 608 E. 12th Street, Washington
27889

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Daniel Thomas Eglinton (ORS), #8 East Forrest Road, Asheville
28803

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Viorica Elisabeth Tanase (PD), P.O. Box 220, Hubert 28539

CATAWBA

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28613

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Robert Dean Bayliss, Jr. (Student), 1641-G Northwest Boule-
vard, Winston-Salem 27104

Joel Miles Carter (ON), P.O. Box 340, Shelby 28150
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 Magnolia Apts., Winston-Salem 27104
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 27834
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 Salem 27103
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 1-E, Roanoke, VA 24014

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 27514
 Nancy Melinda Hill (Student), 202 Pritchard Avenue, Chapel Hill
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 Landing Station, Chapel Hill 27514
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 Mark Harris Lerner (Student), Box 2744, Duke Medical Center,
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 Durham 27710
 Linda Marie Raines (Student), 39-H Laurel Ridge Apts., Chapel
 Hill 27514
 Mitchell Dennis Shub (PD), UNC, Burnett-Womack Bldg. #310,
 Chapel Hill 27514
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 27705
 Jennifer Elaine Taylor (AN), Box 3061, Duke Medical Center,
 Durham 27710
 Willard David Wilcox (OPH), 911 Broad Street, Durham 27705
 William Walter Woodruff, III (Resident), Box 3286, Duke
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 ston-Salem 27103
 Elizabeth Rankin Vaughan (EM), 8058 Deverow Court, Lewis-
 ville 27023

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 boro 27401
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 422 Peacock Street, Ahsoskie 27910

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 27330
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 lotte 28211
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 ville 27834
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 School of Medicine, Greenville 27834

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 28358

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David Clifton Powell (GS), 1108 Dresser Court, Raleigh 27609
Roger Bivins Russell (PS), Cameron Village, 233 Bryan Building, Raleigh 27605
Barry Neil Straus (AN), 2609 Kingsley Road, Raleigh 27609

WATAUGA

Luis Nicholas Hernandez (AN), P.O. Box 1493, Boone 28607
Arnold Oliver Welden (FP), 124 Wildwood Lane, Boone 28607

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Richard James House (OTO), 1207 E. Holly, Goldsboro 27530

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In Memoriam

Hans Lowenbach, M.D.

The North Carolina Neuropsychiatric Association lost a long standing Fellow and dear friend when Dr. Lowenbach passed away quietly in his home on October 19, 1983. He served as delegate to the Assembly of District Branches and was president of the North Carolina District Branch (NCNPA) in 1963.

Hans was born on January 31, 1905 in Duisburg, Georgia. He had his medical education at the University of Hamburg and had his internship and part of his residency in Germany with some of his studies being at the Kaiser Wilhelm Brain Research Institute in Berlin. He completed his psychiatric training at the Phipps Psychiatric Clinic of the Johns Hopkins Hospital in Baltimore, Maryland. He was among the first faculty members of the Department of Psychiatry at Duke University in 1940. He served in the U.S. Army Reserve in 1949-1951 and then became Commander of the U.S. Army Reserve Unit in Durham, North Carolina until his retirement as Colonel in 1969. He was a

Professor of Psychiatry at Duke University and had over sixty publications. Hans became known as a distinguished teacher and role model for medical students and psychiatric residents. After his retirement from Duke University in 1975, he continued his contact with students and training until 1982. He was respected by all who were privileged to know him as students, trainees and peers because of his fairness, expertise in evaluation of the patient and dedication to teaching. His wisdom, warmth, and tolerance for his fellow man will be missed by all of us who knew him.

Dr. Lowenbach is survived by his wife, Eileen Sullivan Lowenbach; three daughters, Christine Shore of Portland, Oregon, Torry Lowenbach of Toronto, Canada and Trude Lawrence of Atlanta, Georgia; and two sisters, Hilda Lowenbach and Trude Lowenbach, both of Dusseldorf, West Germany. The family has requested that those wishing to contribute to Hans' memorial send contributions to Dr. Hans Lowenbach Memorial Fund, Box 3701, Duke University Medical Center, Durham 27710.

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Letters to the Editor

Affective Sickness

To the Editor:

Dr. Freedman's observations (*NCMJ* 45:155-156, March 1983) of the signs and symptoms of depression agree, in most part, with those accepted by the American Psychiatric Association. He obviously is an observing and concerned physician, so I find it incongruous that he states that "... the treatment is not that of persons but rather of their neurochemical processes." Would it not be best to treat the person and the neurochemical process simultaneously? Does Dr. Freedman truly believe that "detailed personal histories are not needed ...?"

James L. Mathis, M.D.
Department of Psychiatric Medicine
East Carolina University
Greenville 27834

Hematologists 1, Cardiologists 0

To the Editor:

I was rather surprised at last week's Medical Conference to have one of Duke's erudite cardiologists attribute the discovery of the physical findings of aortic insufficiency to D. J. Corrigan. Dr. Thomas Hodgkin published a good account of aortic insufficiency three years before Corrigan wrote about it. The paper, entitled "On Retroversion of the Valves of the Aorta," appeared in the *London Medical Gazette* on March 7, 1829. Corrigan's paper was published in 1832. The following two quotations are from the paper by Hodgkin:

Thou wilt probably recollect having pointed out to me, a few months ago, a particular state of the valves of the Aorta, which, by admitting of their falling back towards the ventricle, unfits them for the performance of their function. The specimen ... was first observed by thyself, exhibits this derangement in a well-marked manner.

In defining the antemortem findings he noted that

In diseases of the aortic valves, auscultation often detects a prolonged and perverted sound, such as has been compared to the stroke of a saw, the puff of a pair of bellows or the action of a rasp.

R. Wayne Rundles, M.D.
Department of Medicine
Duke University Medical Center
Durham 27710

Editor's reply: This hematologist can see beyond the blood cells.

The Extinct Physician: Heads

To the Editor:

I now read the *Journal* from cover to cover. Thanks so much for the new and interesting format.

Dr. Hadler's article on "The State of Medicine in 1983: The Extinction of the Physician" in the February 1984 *Journal* was one of the most instructive I have yet read on the present state of the practice of Medicine everywhere.

As an old friend and distinguished colleague of mine has always said, "What this patient needs is a Doctor!"

Patients still respond to kindness, listening, being seen at the time of their appointments, personal unhurried attention, history or interval note taking by their doctor, reasonable fees and thorough physical exams when seen at the office or hospital.

Joseph B. Stevens, M.D.
1017 Professional Village
Greensboro

The Extinct Physician: Tails

To the Editor:

The article "The State of Medicine in 1983: The Extinction of the Physician" by Nordin M. Hadler, M.D. of the Department of Medicine and Microbiology, University of North Carolina School of Medicine, seems to exemplify its own problem: i.e., the ivory tower isolation of medical school educators whose attitudes are unrelated to reality and who are often unaware of the trends of American medicine.

The author is apparently uninformed of his own institution's efforts in producing not just "primary care internist-pediatrician" clinicians, but scientifically based, intellectually stimulated, patient-oriented and caring family physicians. The article to me is ten years behind the response of the legislature and the general public in demanding and now in receiving well-trained, compassionate, people-oriented physicians.

"An ill individual may still turn to and value his physician." Family physicians are "skilled," "highly trained" and "scientific" and they can and are "expected to help patients cope with the impact of their disease in their life."

True, "minions have been cultivated to supplement the doctor" but to supplement, not supplant. The ethic that all physicians should live by is "You can't learn it all, but you can never cease trying," for as I was taught at Duke twenty years ago, "half of all you learn today will be later proven untrue, but I cannot tell you now which half this will be."

In 1974 this article would have been a foresighted observation; the academic community's attitudes still remains ten years behind. The social realities are that the public wants, needs and demands such physicians. Family Medicine is responding to this call. Your elegy for the "health care system" in America is not appropriate and issued too late.

The isolated, investigative academician is the only one who cannot identify "a niche, need or role for a personal physician any more."

America is maintaining a cadre of providers of health

care. They are the primary care internists, pediatricians, and family physicians.

Harry H. Summerlin, Jr., M.D.
944 Tunnel Road
Asheville 28805

Another Man's Poison

To the Editor:

As an old hand in this "poison stuff," I find Ronald Mack's *Toxic Encounters* both informative and hilarious.

Jay M. Arena, M.D.
Duke University Medical Center
Durham 27710

Emergency Use of Epinephrine Restricted

To the Editor:

In regard to a recent letter to the editor (*NCMJ* 45:137-138, February 1984) regarding non-physicians who have been trained to administer epinephrine in emergency situations, I believe it should be called to the attention of your readers that North Carolina General Statute 90.143-509 permits the Board of Medical Examiners to approve individuals who have successfully completed appropriate training programs to administer epinephrine to persons who suffer a severe adverse reaction to insect stings only. The statute goes on to restrict such an administration only "in the absence of the availability of physicians or other practitioners who are authorized to administer the treatment."

A. T. Pagter, Jr., M.D., President
North Carolina Board of Medical Examiners
Raleigh 27601

Corporate Restructuring

To the Editor:

I have had occasion to read the January 1984 issue of the *North Carolina Medical Journal*, and particularly the article by Paul M. Wiles on "Corporate Restructuring: One Answer to TEFRA's Challenge."

I was most impressed with the quality of the article and with the excellent manner in which Mr. Wiles addressed the issues. I know that there are several different ways in which hospitals can restructure, but certainly the reasons and benefits are clear and Mr. Wiles describes them well.

An interesting situation has occurred over the past two to three years, and that has been the need for hospitals to reconsider restructuring that was accomplished in 1981 and 1982 to bring the organizational arrangements in line with the Tax Equity and Fiscal Responsibility Act, and in particular with the changes in the type of competition that exists. For example, our institution went through a restructuring in late 1981 and early 1982, but has felt the need now in late 1983 and 1984 to re-evaluate our initial methodology and ensure that the organizational structure reflects best the changes in the marketplace.

I agree wholeheartedly with the need for professional consultation and especially heavy involvement of many members of the board and medical staff. Hospitals that ignore the concerns and issues that the medical staff bring up will find that the corporate restructuring is counter-

productive rather than an aid to them as they move through the challenging times ahead.

I look forward to reading more articles on such critical issues in your journal.

Robert F. Burgin
President
Memorial Mission Hospital
Asheville 28801

Warts and All

To the Editor:

The response to our article on warts published in the *North Carolina Medical Journal* (44:730, November 1983) has been overwhelming. The article was picked up by the various news agencies and apparently circulated throughout the United States.

Wart sufferers from Georgia to Hawaii have written with their own personal experiences with warts and have suggested cures that even Dr. Callaway had never heard of. It is evident from these letters that patients enthusiastically support the notion that the power of suggestion is efficacious not only in wart therapy but in medical care in general.

From the response I have received I am of the opinion that warts are one experience that unites all mankind. An experience with warts is something we all have in common.

I am enthusiastically collecting the suggestions from your readers. The papaya seeds from Hawaii, the bee pollen from Georgia, the magic stone from New York, and many other remedies are being carefully saved for posterity. I would love to hear from anyone who has a treatment they think we should know about.

Claude S. Burton, M.D.
VA Medical Center
Durham 27705

From the Committee on Communications

To the Editor:

The blue section in the October 1983 issue of the *NCMJ* regarding resources for the visually impaired has stimulated the Committee on Communications to expand its scope.

We are exploring the feasibility of producing the Society's educational pamphlets for the public in braille. We hope to encourage the N. C. Pharmaceutical Association to make prescription labels in braille available in most cities.

Physicians in private practice should encourage visually impaired to place their medications in boxes divided into compartments to facilitate taking drugs on a daily/weekly basis accurately. These simple homemade devices can be fashioned to suit the individual needs of each patient.

We welcome additional ideas from our colleagues; please forward them to our Communication Director, Tom Bennett, at Society headquarters.

Elizabeth P. Kanof, M.D.
Chairman, Committee on Communications
North Carolina Medical Society
Raleigh 27611

From the Managing Editor:

I would like to share some good news. For the first time since I've been Managing Editor of the *North Carolina Medical Journal* the revenue from national and local advertising will cover the cost of composing, printing, and binding this issue of the *Journal*. I hope each of you will remind your friends that the *Journal* is an effective advertising medium and mention the *Journal* when you deal with any of our present advertisers.

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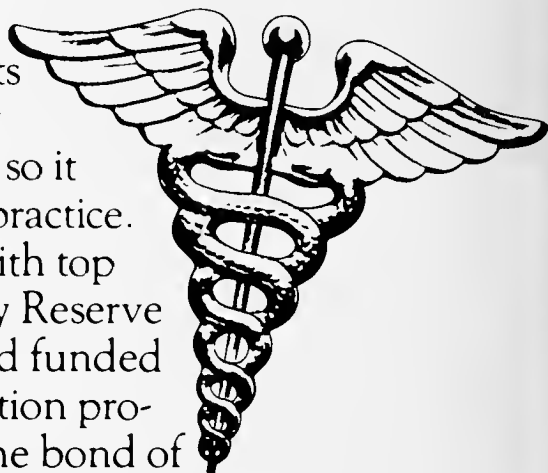
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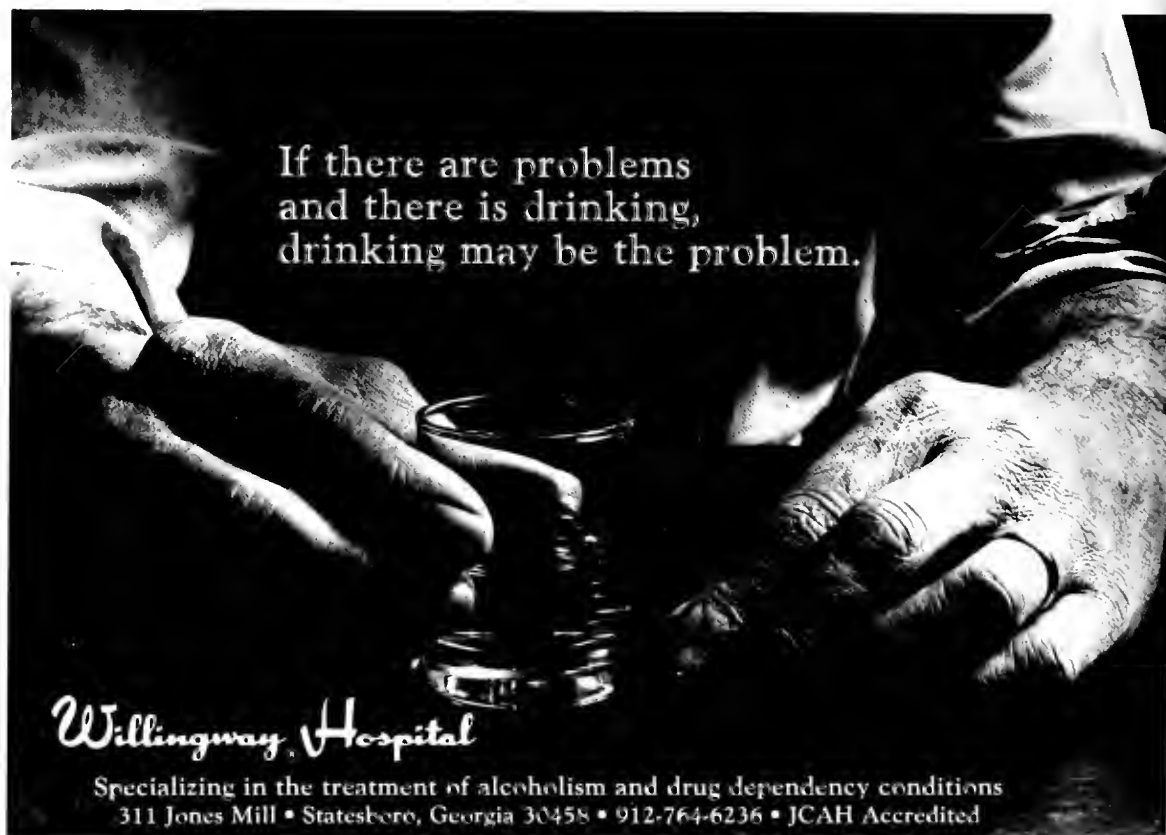
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Black Dermographism by Lester Fahrner, M.D., page 395

The woman in these photos displays the interesting, clinically insignificant finding of black coloration on cheek and forehead (top) and fingers (bottom) after rubbing with gold rings.



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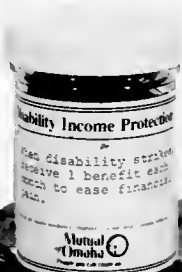
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Renal Dialysis for Kidney Failure in North Carolina: History, Practice, and Lessons

Robert A. Gutman, M.D.

RENAL failure entitles a patient to federal funds for his therapy with only one provision, that he or a member of his family has participated in our Social Security system. Since the law providing this entitlement was passed, the number of dialysis patients in the United States has grown from approximately 7,000 to over 70,000. With this population surge, costs have gone from about 0.5 billion to nearly 3 billion dollars per year. Kidney failure is the only disease for which there is an unrestricted entitlement to care in the general community.* No other chronic disease is similarly covered: not liver failure, advanced heart disease, leukemia, sickle cell anemia, cerebral palsy, cancer, stroke or myocardial infarction. In all other instances, entitlement to government medical assistance is based on the individual's present or past role in society. For example, persons over age 65, military personnel and their dependents, veterans, Indians, Merchant Marines, postal workers, and many who are recipients of welfare programs are covered by one or another form of federal or state medical insurance. The End-Stage Renal Disease (ESRD) Program provides treatment for a single catastrophic disease and may be a harbinger of programs to come, possibly including liver and heart transplantation and replacement of Factor VIII for hemophiliacs.

In North Carolina this unique federal program has some of its own distinguishing characteristics. For example, the North Carolina End-Stage Renal Disease Program differs from that of our neighbors by being more cohesive, by involving patients to a larger degree, and by its freedom of control from outside large-chain dialysis companies. In this article I shall trace the political origins at both federal and state levels of our program and give my interpretation of what lessons are extractable from our experiences. The story is interesting because it contains features of possible future government involvement in large-scale funding for other catastrophic diseases, yet the experience is small enough to be told in some detail.

An early warning to the reader is warranted. Only those individuals on either political extreme will be able to ex-

tract a single crisp, clean lesson in this account. For those with an unqualified commitment to full financial assistance for medical therapy, the government's program will seem tentative, half-hearted, and unnecessarily complex. On the other hand, those who view government medicine as an anathema will view the cost overrun and the crippling entitlement expansion as a clear vindication of their principles.

Origins of the Program

Hemodialysis is nothing new. During the Nazi occupation of Holland, Dr. Willem J. Kolff successfully developed a system for pumping blood through an outside-the-body circuit. The lengths of tubular semipermeable cellophane were actually German sausage casing. Kolff brought his apparatus to the U.S. before 1950, and within a few years clinical hemodialysis became a practical method of treating acute renal failure. But the revolutionary character of hemodialysis began only around 1961 when Dr. Belding Scribner demonstrated the feasibility of continuous maintenance dialysis. Originally, the treatments cost approximately \$30,000 (1962 dollars) per year. The early patients were relatively young and had no problems except kidney failure; indeed, of the first three patients chosen in 1960 for these experimental procedures, two lived more than 10 years and one is alive today. Although Scribner realized that his achievement raised difficult social issues, he began early in the technologic development to seek equitable forms of funding. In sharp contrast, some prominent members of the academic nephrology community expressed grave doubts about the wisdom of proceeding with any government funding. They likened this therapy to the iron lung and its use for poliomyelitis victims: a "halfway therapy." Suggesting that the money would be better spent on research, they made an oversimplified analogy to the successful development of polio vaccine, which had virtually eliminated the need for iron lungs. So it would be with kidney research, they claimed; soon dialysis machines would not be necessary.

But the forces of human nature were at work. Seattle began to raise money for a few of its citizens and by 1962 the personal dilemma of choosing which candidates would receive the scarce funds was sensationalized by *Life* magazine. Money from the federal government began to trickle in shortly after that, first through the establishment of

From the Department of Medicine, Duke University Medical Center, Durham 27710.

* Venereal diseases carry disease-specific entitlement, but they are generally acute illnesses and care is free only at specific sites, such as community health centers. Leprosy and tuberculosis entitle a patient to care only at government institutions.

Veterans Administration Centers in 1963, and next through the establishment in 1964 of demonstration projects under the Public Health Service. From 1964 to 1967, these demonstration projects were by and large successful. Patients were living longer and some even were returning to work.

The United States was already on the slippery slope of granting nearly universal entitlement to government funds for dialysis, with transplant therapy soon to be included. The first five years of this evolution were quiet. Although U.S. Senator Henry Jackson (D-Wash) proposed expansion of the program on several occasions, neither the House nor the Senate took action until 1969. First, Congress expanded the role of the Regional Medical Programs to include kidney disease as well as cancer, heart disease, and stroke. Under this legislation, the Public Health Service provided funds for community dialysis centers. Shortly after that, Congress began to hear testimony from relatively healthy patients, one of whom actually carried out a home dialysis treatment in a congressional hearing room. Important senators such as Jackson (and later, Vance Hartke) assured their fellow lawmakers that money for dialysis and transplantation would be recouped easily by virtue of the savings of welfare payment to families of rehabilitated patients. Consequently, Congress passed legislation in 1972 entitling Social Security participants and their families 80% support for treatment for end-stage renal failure when "medically determined" to be necessary. The character of the program immediately began to change. Medical determination became simply "making the diagnosis of kidney failure." Under the relatively generous reimbursement policies set out at that time, commercial competition flourished and the actual cost of treatment began to fall, leaving room for large profits for commercial operators. Large-chain companies came into existence, some seemingly overnight. The machines, the dialyzers, the disposable equipment and much of the associated technology improved considerably under the dual stimuli of federal money for research and federal money for services. The dominant characteristics of the patients in the program began to change dramatically as older and sicker patients with the diagnosis of end-stage renal disease were admitted.¹ These patients had many other medical problems in addition to renal failure.

North Carolina Developments

Here in North Carolina the end-stage renal program had already acquired a unique character. Before the passage of the 1972 Social Security legislation, leaders of the nephrology training programs at Duke and the University of North Carolina worked closely with key members of the North Carolina legislature. As a result of their efforts, aided considerably by a prominent legislator who was himself a renal failure patient, seed money was set aside to aid patients with the costs of home dialysis or transplantation. This money prompted the development of a "renal office" in the State Department of Human Resources which relied heavily on the professional advice of prominent nephrologists in academic medicine and in clinical practice. Statewide cooperation in planning and patient assistance emerged from these efforts so that when the federal program appeared, North Carolina already had the mechanism

to deal with the new rules and the new money.

For example, Congress determined that the nation should be divided into 32 End-Stage Renal Disease networks, each network to consist of all the providers of dialysis and transplantation services within its defined boundaries. The reason for establishing networks was to provide local Professional Services Review Organization-styled systems for monitoring the quality and cost of therapy. In many instances, the geographical boundaries of a network were to include more than one state or several pieces of several states. Thanks to our early preparations and our leadership, North Carolina, originally designed to be divided among two networks, was finally made a network of its own, thus avoiding confusion and overlapping areas of responsibility. Consequently, our network (No. 21) assumed many of the advisory functions previously reserved for the State Department of Human Resources including important roles in planning the location and character of treatment centers during the first years. This *advisory function* became more important for many physicians and patients than the *quality assurance functions* which the federal government expected to dominate. Our tradition of cooperation held as new facilities opened under the guidance of our state's program directors, some of whom were graduates of training programs at Duke and UNC. Owing to circumstances, example, and planning, most of the North Carolina units became owner-operated rather than franchise operations for large-chain dialysis companies. In other parts of the country, most of these large companies (some "profit" and some "non-profit") had developed Center dialysis to the near exclusion of home treatment options. By contrast, most of the owner-operators of the North Carolina dialysis programs have used these options for fully a fourth of their patients. North Carolina has been the third or fourth most frequent user of home dialysis on a per capita basis and yet has one of the largest fractions of "for-profit" dialysis units — giving lie to the premise that for-profit dialysis led inevitably to overuse of the Centers and larger profits. More recently, the government has removed virtually all financial advantage for in-Center dialysis. This will have little impact in North Carolina because of the pre-existing rate of home dialysis usage.

Current Practices

By 1978 the present dominant characteristics of the federally funded End-Stage Renal Disease Program were becoming clear. Universal funding and diagnosis-determined entitlement were being translated into an increased willingness to use dialysis or transplantation even for patients with far-advanced age and other illnesses. The average age of patients on dialysis was rising, as it continues to rise, by nearly one year with each passing year of the program. The number of new patients starting dialysis was therefore rising also; new patients in 1978 were about 60 per million versus the current rate of well over 80 per million. Another feature to emerge was the uneven distribution of patients among the different communities. Because of the striking predominant risk of end-stage renal disease among Blacks (figure 1), communities with a large fraction of Black citizens had far more patients than did other communities. Today, these communities are

END STAGE RENAL FAILURE PROGRAM INCIDENCE (NEW STARTS EACH YEAR) 1978-1981

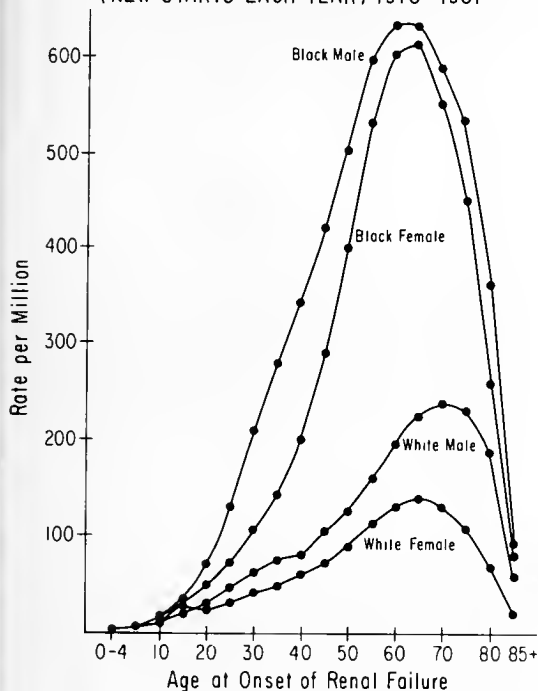


Figure 1. ESRD Program incidence (number of new starts per year per million population of same age, sex and race) displayed by demographic status. Data are from the HCFA Medical Information System.

approaching 500 persons on maintenance dialysis programs for every million in the population.

While it is true that each patient on dialysis does increase a facility's revenue, the principal reason for the widened admission policy nationwide was not profit, as some have claimed. It was the normal human reluctance to stand by while death overtook a person with a "treatable" disease. Each nephrologist can remember a patient everyone said was too sick to benefit from dialysis treatment but who has

Table 1

Characteristics of Patients on Maintenance Hemodialysis Treatment Before and After the ESRD Legislation of 1972 (Adapted from Evans et al.¹)

Year	1967	1978
Estimated ESRD population	850	46,568*
Percent male	75	49
Percent white	91	64
Percent over age 54	9	48
Percent disabled	13	54

* Number enrolled under all federal programs (Health Care Financing Review, Vol. 4, page 91, 1983). As of December 1982, the combined networks reported that 67,763 Americans were on dialysis treatment.

nevertheless surprised us by returning to a near-normal life while on maintenance dialysis. The owner-operator and academically-directed facilities of North Carolina were not immune to the desire to prolong life. Their conservative streak, however, fostered by tradition, network participation, and the tension of having to deal with severe morbidity, led to a somewhat more balanced approach to the decisions regarding patient admission. Recognizing that dialysis may only prolong dying, one physician said, "Not all terminally ill patients with renal failure have to do their dying on maintenance dialysis." Other physicians commented that they spent more time explaining the rigors and the disappointments of dialysis to very sick patients and their families than they might have spent had they admitted them to their dialysis program.

This conservatism seems to find less expression in statistics in the country overall. In 1981 Evans et al compared the characteristics of dialysis patients before and after funding for end-stage renal disease became law (table 1).¹ These expanded admission criteria were the primary cause for the unanticipated cost increase of the program. The original intent of the law was to provide funds for those who could benefit from, but could not afford the cost of, treatment. Once enacted, dialysis and transplantation became a universal right for all patients with renal failure irrespective of their associated illness. Even with the inclusion of these unusually sick people, the per capita cost of the treatments rose slower than the general inflation rate (table 2). But the

Table 2
Change of Per Capita Cost* for ESRD Treatment as Compared with General Inflation Rate

Year	Cost Per Patient Per Year (Dollars)	Percent Change %	General Inflation Rate %	Inflation Corrected Change %
1973	13,740	—	—	—
1974	14,880	8.3	8.8	- 0.4
1975	16,472	10.7	9.3	+ 1.3
1976	17,395	5.6	5.2	+ 0.4
1977	18,679	7.4	5.8	+ 1.5
1978	18,918	1.3	7.4	- 5.7
1979	18,759	-0.8	8.6	- 7.2
Average Change		5.4	7.5	- 1.7
Total 6 Year Change		36.5	63.4	- 16.5

* "Costs" are payments by the Health Care Financing Administration (HCFA) for all entitled patients' dialysis, transplantation, and hospitalization. The payments are not necessarily for an entire year of service as not all the patients are on the program for an entire calendar year. Nor do costs equal charges or costs to the facilities. In general, "costs" are 80% of "allowable" charge. However trends are considered useful data. Table is calculated from HCFA data and from the 1982 Economic Report of the President.

burgeoning number of enrollees more than overcame the reduced individual cost and the program cost soared.

Government Attempts to Control Costs

In an early effort to control costs, the Health Care Financing Agency recommended to Congress the enactment of a series of cost-control efforts. One of the first attempts was to undertake a social experiment limited to a few selected areas of the country. North Carolina included. This experiment, the Paid Aide Study, was intended to discover if offering small payment to families or friends in order to encourage patients to undertake the presumably less expensive home dialysis would save the country money by reducing the size of dialysis facilities. The experiment failed. The money for paid aides neither increased the frequency of the use of home dialysis nor reduced the cost of the program; in fact, the cost probably increased. Another effort from the Health Care Financing Agency was the requirement that local networks set numerical "goals" to increase the frequency of home dialysis usage and transplantation. Each network set its goal slightly above that which it was already achieving — a perfunctory exercise. In North Carolina we already had a relatively high frequency of home dialysis, so our goal was appreciably higher than that of most other areas.

The futility of these inducements and goals led Congress in 1982 to enact a fiscal policy reminiscent of Diagnostic Related Groups (DRG)-styled control of Medicare hospital costs. Now dialysis units are paid the same amount of money for all patients regardless of whether they are being treated by hemodialysis or peritoneal dialysis; and whether at home or in the Center (the amount is less than they previously received for just the in-Center hemodialysis treatments). This "composite rate" is intended to shift enthusiasm toward the allegedly less expensive modes of therapy, for example home dialysis. This policy is not without appreciable unintended risks. Facility costs also could be reduced by hiring fewer people or making do with less expensive equipment and supplies. Costs may also be reduced by refusal of very marginal, high-cost patients who have other serious diseases. With these concerns in mind, some members in the federal government are now re-emphasizing the networks as possible monitors of the "quality of care" of patients — a task the network, a facility-dominated organization, has always felt some discomfort with.

Data Problems

And what about the patients? How are they doing? Congress mandated a "Medical Information System" when the entitlement law was passed. The Medical Information System promised to continue the very good volunteer national registry that until then had been the responsibility of the Research Triangle Institute here in North Carolina. But the federal government's registry failed to maintain any useful assessment of patient outcome. More recently, the Medical Information System has been able to provide Congress with some assessment of the number of patients and the cost of dialysis. Even for this information, it has depended heavily on network participation. This unfortunate state of affairs has been the subject of critical editorials in prominent

medical journals. For example, the *New England Journal of Medicine* asked in an editorial:² "Where are the data?" and reflected with despair on the fact that the European registries, despite multinational boundaries and polylingual barriers, were able to operate effectively to give their end-stage renal disease community a reasonably accurate assessment of the outcome of various groups of patients.

On its own, and despite initial opposition from the Health Care Financing Agency, the North Carolina network has begun to classify its end-stage renal disease patients by co-morbid status, as well as by age, sex, and race, and to track them prospectively. Within a year, our area may be able to begin to answer the question: "How are the patients doing?" But federal threats to cease funding the networks may undermine this effort and leave us with an expensive end-stage renal disease program costing well over 2.5 billion dollars per year — a cost that is likely to grow to twice this size — for which the government is scarcely able to give an account of the outcome of the patients the program serves.

On the brighter side, there are indications that many patients are doing well. In our own survey, we learned that two-thirds of working-age men previously employed who had had at least one year of college education, were working full- or part-time.³ And of course no one can measure the social value of extending the lives of grandparents or family members several years past the expected date of death from uremia, even if gainful employment has not been achieved.

Research Funding — A Useful Spin-Off

Moreover, the end-stage renal disease program has maintained general awareness of the importance of treating patients with renal insufficiency before they reach "end-stage." This awareness has been translated to making research funds available and is beginning to pay off. Recent work points toward the possibility of slowing the rate of progression of renal insufficiency.⁴ The important insights gained through this research include the need to control blood pressure, to reduce the work of the kidney by dietary adjustment, and to control secondary hyperparathyroidism. Arguably, most of our improvements in approach to patient care owe their development to the research stimulated by the existence of this program.

What Have We Learned?

There are lessons to be learned from this experience. One of them certainly is that once a half-way technologic breakthrough occurs in medical management, it will probably find its way into our repertoire of choices and has a very good chance of being funded. The political process and climate will determine this funding. Once funding occurs, the program is likely to change, especially with regard to the patient inclusion criteria. These events will give rise to a bureaucracy that struggles to contain costs without mandating strict admission criteria. Such a bureaucracy is likely to feel pressure to make frequent policy changes and is doomed to become quite cumbersome. The new money will also give rise to a new industry, new bases of wealth and, thankfully, some new knowledge.

Rising expectations will be the dominant feature of a

funded program. In part, these expectations are patient-specific and will lead to the inclusion of marginally (from a medical point of view) acceptable patients. In part, these expectations will be met.

The end-stage renal disease program has been neither all bad nor all good. The principal features of new programs will probably evolve along similar pathways. In the next decade, we will very likely see funding provided for the care of patients with other diseases. If Congress accepts the advice of some of the enthusiastic surgeons who are currently doing very well with the care of selected patients in their relatively small programs, funds will be provided for patients with liver failure. The initial intent will be to offer this treatment to children with absent main biliary ducts but the regulations will appear to allow inclusion of people with other diseases (possible including cancer and alcohol-induced cirrhosis) and older people. New questions will arise: Will the patients receive government funding while awaiting a cadaver graft? Will a patient whose graft fails continue to receive government funding until a new graft becomes available? When is a patient certified to be on the

"waiting list" if the inclusion on that list makes him eligible for funding? Once again the government may try unsuccessfully to control total program costs without acknowledging that enrollment size is the real culprit — not individual cost. We can anticipate that national data on patient outcome will be poor unless a private volunteer system arises very quickly. The experience will again be neither all good nor all bad, but our reading of the history of the origins and practice of the end-stage renal disease program ought to allow us to anticipate some of the policy problems that are likely to be encountered.

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Lyme Disease in North Carolina

John L. Harshbarger, M.D., William J. Yount, M.D. and Robert W. Warren, M.D., Ph.D.

LYME disease, originally named for an endemic area in Connecticut, is a tick-borne spirochetal illness characterized by a distinctive skin lesion, erythema chronicum migrans, by arthritis, and less commonly by neurologic and cardiac abnormalities.^{1, 2} Thus far, more than 500 cases have been described, primarily in southeastern Connecticut, New York, Massachusetts, Rhode Island, Wisconsin, Minnesota, Oregon and California.³ Recently, two patients from North Carolina with the classic skin rash of erythema chronicum migrans have been described.⁴

The purpose of the present report is to describe two atypical but serologically proven cases of the disease originating in North Carolina. The first patient, a 42-year-old woman with long-standing ankylosing spondylitis, presented with constitutional symptoms; the second, a child, was originally thought to have juvenile rheumatoid arthritis.

Now that the clinical spectrum of Lyme disease is more fully defined, a diagnostic serologic marker is available, and appropriate therapy has been documented to attenuate the primary disease and prevent secondary and tertiary manifestations, physicians and patients in North Carolina must have a high index of suspicion in order to appropriately identify and treat patients with this disorder. We predict that Lyme disease, like Rocky Mountain Spotted Fever, may in fact be common in North Carolina, but has often gone unrecognized.

Case 1

A 42-year-old research analyst with an 18-year history of HLA B27 positive ankylosing spondylitis remained well on indomethacin 75 mg daily until May of 1983 when she developed a right pretibial red papule which expanded to about 15 cm and then resolved spontaneously over about 7 days. Shortly thereafter she developed low grade fever, sore throat, headache, malaise, fatigue and anorexia and began to lose weight. She did not recall contact with a tick, although she worked daily in her vegetable garden; she had not traveled outside North Carolina in the preceding year. Symptoms persisted and she first sought evaluation in June 1983.

Examination revealed only a slight fever of 37.6°C, a 4.5 kg weight loss, mild pharyngeal erythema, and a 0.5 cm freely movable, nontender right posterior cervical lymph node. Complete blood count, urinalysis, 17 chemistry panel, throat culture and chest x-ray were normal. She was empirically treated with tetracycline 1.0 g per day for 7

days. Through July and August low grade fever, malaise, fatigue, headache and anorexia persisted and total weight loss reached 19 kg. Physical examination remained otherwise negative, without physical stigmata of reactivation of the spondyarthropathy. Abdominal ultrasound was normal as was a lumbar puncture. Spinal fluid revealed only 2 lymphocytes/mm³ and was negative for bacterial, fungal, mycobacterial, and viral organisms. Negative serologic studies included antistreptolysin O; *Salmonella* O antigens A, B, C and D and H antigens A, B, C, D; Leptospirosis; Toxoplasmosis; Rubella; Rubeola complement fixation and hemagglutination inhibition; Monospot; *Mycoplasma* complement fixation; Cytomegalovirus; Herpes simplex virus; Respiratory syncytial virus; Eastern Equine Encephalitis; Western Equine Encephalitis; Saint Louis Encephalitis; Cryptococcal antigen; Rickettsial agglutinins for *Proteus* OX2 and OX19 and FTA Abs. The indirect immunofluorescence test for *Ixodes dammini* spirochete was positive at a titer of 1:256 on 8/11/83 and at a titer of 1:512 one month later.

When the serologic study for Lyme disease returned positive in a diagnostic range ($\geq 1:128$), she was again treated with tetracycline 2.0 g/day for 20 days. Two days after the institution of this therapy she experienced a Jarisch-Herxheimer-like reaction with low grade fever, myalgia and chills. Tetracycline was continued and all symptoms subsequently subsided.

Case 2

A 5½-year-old white boy was well until April 1983 when expanding erythematous macules appeared on the dorsal aspect of both wrists and enlarged to 5 cm. These resolved spontaneously in three weeks. In May 1983 he was hospitalized with fever, exudative tonsillitis, and an acral petechial rash. His parents had removed multiple ticks from him daily over the preceding two months.

There was no adenopathy or organomegaly. The white blood count was 22,000/mm³ with 60 percent lymphocytes (many atypical). Liver function tests were normal. OX-19 and monospot serologies were both reported as "positive." He was treated with intravenous penicillin and tetracycline and his rash and white blood cell count improved.

He returned to his private pediatrician in June 1983 with a chronic diffuse papular rash, recurrence of fatigue, and swollen tender ankles and elbows. He was rehospitalized to rule out rheumatic fever. His temperature was 38°C, pulse 96, respirations 24 and blood pressure 114/80. He had minimal cervical adenopathy, a benign systolic murmur at the left lower sternal border, and a barely palpable spleen. The hemoglobin was 12.1 g/dl and the white blood cell

From the Divisions of Rheumatology and Immunology, Departments of Medicine and Pediatrics, University of North Carolina School of Medicine, Chapel Hill 27514.

count was 9,400 with 57 polymorphonuclear leukocytes, 1 band, 39 lymphocytes, 1 monocyte, and 2 basophils per 100 cells. The Westergren sedimentation rate was 40 mm/hr. Twelve chemistry panel was normal, as were the electrocardiogram and chest x-ray. The *Proteus* OX-2 agglutinins were positive at 1:160. The ASO titer was 12 Todd units. The VDRL and rheumatoid factor were negative. He was discharged on 1800 mg of aspirin daily. Soon after, he developed arthritis of the right wrist and was referred to North Carolina Memorial Hospital for rheumatology consultation with a provisional diagnosis of juvenile rheumatoid arthritis.

His history was otherwise totally negative for abnormalities of skin or hair, mucosa, eyes, cardiorespiratory, gastrointestinal, genitourinary or neurologic systems and was negative for symptoms in other joints or the back. At the time of consultation, all joint symptoms had resolved and the physical examination was entirely normal. Slit lamp examination was negative for uveitis. The hemoglobin was 12.2 g/dl, white blood cell count 7,200 with a normal differential. Urinalysis, Westergren sedimentation rate, rheumatoid factor and antinuclear antibody were all normal. Indirect immunofluorescence test for *Ixodes dammini* spirochete was positive at a titer of 1:128 (IgG). There has been no recurrence of symptoms.

Discussion and Review of Lyme Disease

North Carolina has the highest incidence (22 percent) of cases of Rocky Mountain Spotted Fever occurring annually in the United States.⁵ The present report documents the presence of Lyme disease, another tick-borne disease, in North Carolina. The prevalence of the disease is unknown, but it may well be high and unappreciated. In order to establish the diagnosis of Lyme disease, physicians, other health professionals, and patients must appreciate the variable manifestations of this disorder, have a high index of suspicion, seek serologic confirmation when indicated, and initiate appropriate therapy in order to avoid the chronic manifestations of the disease. The late manifestations may not respond well to appropriate antibiotic therapy begun later in the course. The disorder has been well described in a series of papers which we will briefly summarize.

Both of our cases illustrate some features of the difficulty in differential diagnosis. In neither case were the skin lesions classic for erythema chronicum migrans. Case 1 did not seek medical attention when the skin lesion was present and gave no history of tick bite. Case 2 was initially thought to have Rocky Mountain Spotted Fever, possibly infectious mononucleosis, then acute rheumatic fever, and with the development of recurrent arthritis was thought to have juvenile rheumatoid arthritis.

Approximately 70 percent of patients do not recall a tick bite,⁶ and some may develop Lyme disease without the initial characteristic skin lesion making diagnosis more difficult. Ross and Benach have recently reported a group of "pauciarticular JRA" patients without a history of erythema chronicum migrans who have serologically defined Lyme disease.⁷

Lyme disease was first described in 1975 when several mothers in Lyme, Connecticut questioned the frequent diagnosis of juvenile rheumatoid arthritis in their

community.⁸ The geographic distribution of the disease in New England, the upper Midwest, and on the West Coast, and the seasonal distribution of cases in March through October, with eighty percent of cases occurring in July and August, both suggested an arthropod vector-borne disease. Subsequently a small tick, *Ixodes* species, which feeds on deer and other mammals and rodents, was implicated.³ In the Northeast and Midwest, *Ixodes dammini* has been implicated, on the Pacific Coast *Ixodes pacificus*, and a closely related tick, *Ixodes scapularis*, may be implicated in the South. The tick is small, and the disease may also be carried by the nymph, which is 1 mm long, which would explain the lack of identification by patients.

The pathogen has recently been identified as a new spirochete, thus far designated only as the *Ixodes dammini* spirochete, which has been isolated from 5 of 96 patients, three of the isolates from blood, one from cerebrospinal fluid, and one from the margin of a skin lesion.^{2, 9} With present techniques, the spirochete is difficult to culture and is isolated only on modified Kelly's medium. The spirochete resides in the mid-gut of the tick, and presumably gains entry to man at the site of the bite, which becomes the central papule of erythema chronicum migrans. The percentage of ticks infected varies with the endemic area, with 26 percent of ticks infected in the Lyme area² and 61 percent of ticks infected in the Shelter Island game reserve in New York.¹⁰

The spirochete stains with Giemsa stain and on dark field examination "moves sluggishly and rotates slowly."¹⁰ On electron microscopy it bears some similarity to *Borrelia*; the spirochete is irregularly coiled, 10-30 μ m long and 0.18-0.25 μ m in diameter. Near each tapered end, 4-8 filaments originate in a line along the longitudinal axis.¹⁰ When infected ticks were allowed to feed on rabbits, the rabbits developed skin lesions similar to erythema chronicum migrans 10-12 weeks later which lasted for about eight weeks.¹⁰ All rabbits developed antibodies to the spirochete in titers equal to or greater than 1:1280. Serum samples from patients have been shown to have antibodies to the *Ixodes dammini* spirochete.^{2, 10} IgM antibodies peak at 3-6 weeks in patients with erythema chronicum migrans, in titers equal to or greater than 1:128 in 90 percent of patients and in only three of 80 normal subjects. In 95 patients with late manifestations after several months, 94 percent had IgG titers of 1:128 or greater, while none of 80 normal subjects did.² Thus, the tick-borne *Ixodes dammini* spirochete is the causative agent of Lyme disease. Both of our patients were atypical, but met the necessary clinical and serologic criteria for diagnosis.

Stage 1 disease begins 3-32 days (median 7 days) after the tick bite especially on the thigh, groin, or axilla. Erythema chronicum migrans characteristically begins as a central papule and gradually expands to a median diameter of 15 cm (range 3-68 cm) with a bright red outer border, usually flat, hot and with a burning sensation, with central clearing. The center area may also become vesicular or necrotic, turn blue, or manifest concentric rings.⁵ Other skin lesions include multiple annular secondary lesions, malar rash, conjunctivitis and diffuse urticaria with vasculitis. Median duration is 28 days untreated (range 1 day to 14 months), but only 5-9 days with antibiotic therapy. Secondary le-

sions occur only in untreated patients. They are generally smaller, migrate less and do not have induration in the centers. They may be located anywhere except the palms and soles.

Malaise and fatigue are the most common symptoms that accompany erythema chronicum migrans. Lethargy, headache, fever, chills, stiff neck, arthralgias, myalgias and lymphadenopathy are also frequently observed. These early symptoms and signs are typically intermittent and variable during a period of weeks except for the constant fatigue and lethargy.⁶ These early manifestations are easily confused with viral infections, especially when erythema chronicum migrans is absent or missed. In Lyme disease the most characteristic feature of all the otherwise non-specific symptoms is their intermittent and rapidly changing nature.

Weeks to months following erythema chronicum migrans Stage II disease may occur, with cardiac and neurologic abnormalities. Arthritis is characteristic of Stage III disease, and is seen particularly in patients who are tissue type HLA-DRw2.¹¹ Carditis has been reported in approximately 8 percent of patients with Lyme disease, usually about three weeks after onset, and lasting three days to six weeks.¹² The most common findings are varying degrees of atrioventricular block including first degree, Wenckebach, and complete heart block, which may present with syncope and require a temporary pacemaker. Diffuse myopericarditis and decreased left ventricular function are also known to occur. True valvular disease is not reported. Heart involvement is frequently seen concomitantly with neurologic abnormalities and arthritis.

Common laboratory abnormalities in these patients are elevated Westergren sedimentation rate, IgM, and cryoglobulins containing IgM. Neurological manifestations have been reported in 11 percent of patients with Lyme disease.¹³ The most common pattern is a fluctuating aseptic meningitis with superimposed cranial and peripheral radiculoneuropathy, although encephalitis, chorea, cerebellar ataxia, mononeuritis multiplex, and myelitis have been seen.¹³ Unilateral or bilateral Bell's palsy may occur. Abnormalities appear while erythema chronicum migrans is still present or 1-6 weeks after it has disappeared. During attacks patients have cryoglobulins present in serum and circulating immune complexes as detected by the binding assay for the C1q component of complement.¹⁴ These assays improve or become negative during remission. High dose intravenous penicillin has recently been shown to shorten the duration of meningoencephalitic symptoms in patients with Lyme disease; motor deficits usually require a mean of 7-8 weeks for complete recovery despite antibiotic therapy.¹⁵

Lyme arthritis occurs in about 50 percent of untreated patients from weeks to years after erythema chronicum migrans develops. Most patients have the sudden onset of a recurrent, asymmetric oligoarthritis of large joints, particularly the knees. The initial episode may be brief and migratory. Typically the knees are swollen and warm, but not red. The major functional impairment is difficulty in ambulation. Synovial fluid white cell counts are usually inflammatory but widely variable with 2,000-72,000 cells/mm³ and about 80% polymorphonuclear leukocytes.

Lyme arthritis is often confused with pauciarticular juvenile rheumatoid arthritis (as in our Case 2) except when there is a history of erythema chronicum migrans.⁸ It is important to pursue this history over a period of weeks or even years. Ten percent of patients with Lyme arthritis go on to develop chronic arthritis, usually of the knees, with synovial thickening, pannus formation, and popliteal cysts in a pattern indistinguishable clinically or pathologically from rheumatoid arthritis.¹¹ Morning stiffness, rheumatoid factor, ANA and subcutaneous nodules are usually absent. Tissue typing often reveals HLA-DRw2, whereas HLA-DRw4 is characteristic of adult rheumatoid arthritis and HLA-B27 of spondyarthropathies.

Early in the course of the disease an elevated Westergren ESR is the most common laboratory abnormality. Only 10 percent of patients exhibit anemia or leukocytosis with a left shift. Mild abnormalities of liver function tests may be seen. Elevated total serum IgM is seen in 33 percent of patients.¹ Circulating immune complexes may be present with ECM, and persistently high levels are more commonly seen in patients who develop carditis or chronic arthritis.^{12, 14} Positive cultures for the *Ixodes dammini* spirochete require special medium (modified Kelly's) and the yield is low. Indirect fluorescent antibody titers against the *Ixodes dammini* spirochete have been helpful in difficult diagnostic cases but are available only through the Communicable Disease Center in Atlanta, the State University of New York at Stony Brook (N.Y. Health Department), or through individual research laboratories. [Serum specimens may be mailed to the Division of Rheumatology and Immunology, 932 FLOB Bldg. 231H, University of North Carolina, Chapel Hill 27514.] IgM antibody titers rise initially and reach a peak between the third and sixth week after the onset of the disease. Titers of IgG antibodies rise more slowly and are sensitive and specific during later stages of the disease at titers of 1:128 or greater.²

Treatment

Treatment of early Lyme disease with antibiotics has improved the morbidity, especially by preventing the major late complications of carditis, neurologic sequelae and arthritis. Antibiotics also shorten the duration of erythema chronicum migrans and the constitutional symptoms. Recent studies have shown tetracycline to be the drug of choice, followed by phenoxymethyl penicillin and erythromycin.¹⁶ Specific recommendations at this time in adults are: 1) tetracycline 250 mg p.o. q.i.d. for at least 10 days and as many as 20 days if symptoms recur or persist; 2) in the pregnant female phenoxymethyl penicillin 500 mg q.i.d. for the same duration; 3) erythromycin 250 mg q.i.d. in patients allergic to penicillin. Tetracycline should be avoided in children less than nine years of age because of dental staining; phenoxymethyl penicillin 50 mg/kg/day in divided doses for the same duration, or in the case of penicillin allergy, erythromycin 30 mg/kg/day in divided doses for 15 or 20 days, is recommended. All three drugs have been shown to prevent recurrent erythema chronicum migrans, but occasionally stage II and stage III disease have been seen with phenoxymethyl penicillin and erythromycin, but not with tetracycline.¹⁶ For adults with Lyme meningitis, penicillin G, 20 million units/day in divided

doses for 10 days is recommended, or tetracycline 500 mg q.i.d. p.o. for 30 days in the penicillin-allergic patient.¹⁵

Treatment of the conduction abnormalities of Lyme carditis depends on their severity. Patients with first degree heart block can be carefully followed as outpatients, but those with higher degrees of block should be hospitalized. Patients with complete heart block should have a temporary pacemaker. Prednisone has been used in some patients with carditis in uncontrolled studies. Aspirin or other nonsteroidal antiinflammatory drug is the treatment of choice for chronic arthritis. Intraarticular steroids may be helpful in selected cases, and occasionally synovectomy has been performed in patients with progressive erosive disease.¹¹

Now that the disease has been recognized in North Carolina, an effort at education of health professionals and the public is justified. In addition, surveys of ticks for incidence of spirochetal infection to assess infective risk, and a high index of clinical suspicion are needed in order to identify and treat this fascinating new multisystem disorder caused by the tick-borne *Ixodes dammini* spirochete.

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Percutaneous Fine Needle Aspiration Biopsy of the Lung: East Carolina University School of Medicine/Pitt County Memorial Hospital, 1983

Jan F. Silverman, M.D. and Irwin S. Johnsrude, M.D.

ALTHOUGH the percutaneous approach to diagnosing pulmonary disease was first performed in the 19th century, it was not until the recent development of fine needle techniques that it became a popular diagnostic procedure. Much of its recent acceptance and success can be attributed not only to the development and use of these fine, small-bore needles (20-23 gauge) but also to the application of improved radiologic techniques. These include image intensification, fluoroscopy, and the more recent dramatic development of imaging techniques such as computed tomography (CT). Improved cytologic methods, together with decreasing incidence and severity of complications, have added further impetus to the procedure.¹

Multiple reports have attested to the safety and diagnostic accuracy of the procedure for evaluating pulmonary masses and complex intrathoracic diseases.²⁻⁴ Approximately 450 fine needle aspirations of the lung have been performed at East Carolina University School of Medicine/Pitt County Memorial Hospital over the past five years. The purpose of this paper is to report our experience during the year 1983 and to encourage the use of percutaneous fine needle aspiration biopsy of the lung as a diagnostic procedure.

Materials and Methods

The procedure is similar to methods previously described.^{1, 3} Prior to the study, informed consent is obtained following discussion of the possible complications of the procedure, including pneumothorax and/or bleeding. Mild sedation is usually given. Old and recent films are reviewed with special attention to the chronicity of the lesion, the presence of calcium, and the presence of mass or infiltrate. Identification of multiple lesions, mediastinal lesions, mediastinal or hilar adenopathy, and the true depth of the lesion are often best estimated by means of CT. From these various studies, the most direct vertical approach to the lesion is considered.

The puncture technique consists of positioning the patient so that the lesion closest to the chest wall is facing upward.² The effect of respiration on tumor movement can be seen by fluoroscopic examination. The depth needed for the needle's penetration is estimated and this measurement

is transferred to the biopsy needle at which point the needle is clasped with a rubber-tipped forceps. A cradle x-ray table top or biplane fluoroscopy facilitates accurate needle placement. The skin surface is cleansed with Betadine, local anesthesia is injected into the skin, followed by a small skin stab wound. A 22-gauge (0.6 mm) biopsy needle, held by the rubber forceps at the estimated depth, is then guided into the lesion in a direction parallel to the x-ray beam. It is positioned so that the needle tip and hub are superimposed on each other and on the target. Occasionally, the needle must be angled to avoid skeletal interference. If possible, a puncture is performed above the rib in order to avoid the intercostal artery. There is less chance of pneumothorax if both pleural surfaces are penetrated with one motion and the fissures are not crossed. Often a "gritty" feel is transposed to the needle tip when a tumor or lesion is entered. One can prove accurate placement if the needle tip stays with the tumor on rotation of the cradle top, or if the nodule moves when the needle hub is moved. Sometimes a lateral projection film is necessary to document the needle tip position. When the needle point has been placed in the desired position, the stylet is removed, a 20 ml syringe is attached, and the needle is moved to and fro. Suction is then applied, with further to and fro motion, with the tip within the lesion. The vacuum is released before the removal of the needle, and both the needle and syringe are withdrawn. The syringe is then detached from the needle, filled with air, and reattached, and the needle contents are expressed onto the center of a sterile frosted end-glass slide. An assistant usually helps prepare the slides.

The smear technique consists of compressing the material on the slide with another slide and spreading this material over a small area similar to the preparation used in bone marrow aspirate. The majority of the smears are immediately wet-fixed in 95% alcohol while a few others are air-dried. One or more of the air-dried smears are immediately delivered to the pathologist who performs a rapid modified Wright stain (Diff-Quik).^{*} The staining process takes approximately 20 seconds and the slides are examined wet. The pathologist will then decide on the adequacy of the sample and whether an additional procedure needs to be performed. The pathologist usually gives

From the Department of Clinical Pathology and Diagnostic Medicine and the Department of Radiology, East Carolina University School of Medicine/Pitt County Memorial Hospital, Greenville 27834.

* Available from Harleco, a Division of American Hospital Supply Corp., 480 Democrat Road, Gibbstown, NJ 08027.

Table 1**Indications****Suspected malignancy:**

- other non-operative techniques unsuccessful
- thoracotomy undesirable; patient refuses surgery
- multiple pulmonary lesions
- known primary elsewhere
- non-vascular hilar or mediastinal masses
- pre-op small peripheral nodule

Complicated pulmonary lesions:

- immunosuppressed patients
- complex pneumonias
- abscess; pseudotumor
- diffuse pulmonary disease (?)

Capture viable tumor cells for culture and chemosensitivity testing

Table 2**Relative Contraindications to Percutaneous Needle Aspiration of the Lung**

- uncooperative patient
- severe recent hemoptysis
- bleeding diathesis
- severe pulmonary hypertension
- aneurysm, pulmonary arteriovenous malformation, pulmonary varix
- COPD ($PO_2 < 60$ mm Hg; $< 50\%$ predicted airflow)
- large bullae
- only one functioning lung
- hydatid cyst

Table 3**Cytologic Diagnoses**

Diagnosis	Number
Squamous cell	16
Adenocarcinoma (including alveolar cell)	16
Large cell undifferentiated (including giant cell)	5
Small cell carcinoma	4
Poorly differentiated	5
Metastatic malignant schwannoma	1
Atypical (compatible with malignancy)	5

his preliminary diagnosis in person in the radiology department procedure room where he can review the x-rays and directly confer with the radiologist. The immediate "quick-read" procedure can usually be performed within five minutes. At this time, any additional material can be allocated for further studies including microbiologic examination, cell block and electron microscopy. The remaining 95% alcohol fixed slides are examined within one or two hours and the final diagnosis is rendered. The pathologist contacts both the radiologist and the patient's physician.

Following the biopsy procedure, the patient is checked for immediate and/or delayed pneumothorax and parenchymal or pleural hemothorax. Vital signs are recorded and the patient is observed for hemoptysis.

Indications and Contraindications

Indications for fine needle aspiration biopsy at PCMH are outlined in table 1. The main indication is obtaining a definite diagnosis of a persisting localized lesion of the lung. The contraindications are presented in table 2.

Results

Seventy-four patients underwent 84 biopsies at Pitt County Memorial Hospital in 1983. The age range was 37 to 83 years old with 42 males and 32 females.

Forty-seven definite malignant diagnoses were rendered along with five highly atypical diagnoses. For discussion purposes, both groups are combined to represent 52 positive diagnoses. There were 32 negative cases. Four of the negative cases were later shown to be malignant by histologic examination for a false negative rate of 7.1%. There were no false positives. The sensitivity of the procedure (true positive) was 93% and specificity (true negative) was 100%.

The types of malignancies diagnosed in the 52 positive aspirations are presented in table 3. As noted, 47 relatively specific diagnoses were given with only five patients having a non-specific atypical diagnosis. Of the 16 patients having a histologic examination of their lung lesions, only three patients had discordance of diagnosis for a cytologic/histologic correlation rate of 81.3% (table 4). A number of

Table 4**Correlation Between Cytologic and Histologic Classification**

Cytology	Histology					
	Squamous Cell	Adeno.	Large Cell	Small Cell	Poorly Diff.	Other
Squamous cell	3	1				
Adeno		3				
Large Cell				1*		
Small Cell				1†		
Poorly Diff.	1				1	
Atypical	1	3				
Other						1

* Small cell carcinoma diagnosed initially by bronchial biopsy and aspiration performed the next year to evaluate recurrence.

† Undifferentiated malignancy diagnosed initially by histologic examination with aspiration cytology performed to give more specific diagnosis. Aspiration cytology and electron microscopy of aspirated material gave specific diagnosis of small cell undifferentiated carcinoma (oat cell carcinoma).

Table 5
Complications of 84 Biopsies

Pneumothorax — Total	— 27%
Minor (no tube)	— 17%
Requiring tube	— 10%
Hemoptysis	— 3%
Minor parenchymal bleed	— 2%

the 32 negative diagnoses were relatively specific including two granulomatous diseases (cryptococcus and atypical tuberculosis), one aspergillosis, one abscess, and one pulmonary infarct.

The complications of the procedure are all relatively minor (table 5). The pneumothorax rate was 40% earlier in the year, but declined to 21% following the uniform institution of the "quick-read" procedure with an overall percentage of 27 for the full year. The "quick-read" procedure allows for an answer regarding adequacy of the biopsy sample within several minutes, and made it possible to abandon the previous routine use of multiple punctures considered necessary to assure a diagnosis.

Discussion

The main value of pulmonary fine needle aspiration biopsy is in the diagnosis of malignancy with an accuracy rate of 80 to 95% in most recent series and exemplified by our 1983 experience.¹⁻⁵ A definite diagnosis can be given in most patients with minimal trauma, shorter hospital stay and at lower cost. Patients who are poor surgical risks are saved a thoracotomy and others who are clinically inoperable can receive appropriate chemotherapy or radiotherapy without major surgery performed solely for diagnostic purposes.

Fine needle aspiration biopsies have been shown to be superior to bronchoscopic biopsies and sputum cytology in the diagnosis of radiologic evident lesions.⁶ Sputum cytology

still remains the method of choice for screening patients with early non-radiographically visualized lesions. Bronchial brush biopsy is especially valuable for evaluation of central bronchial lesions. The combined use of all three cytologic sampling procedures can insure the highest degree of accuracy in the evaluation of intrathoracic lesions.

The diagnostic yield of fine needle aspiration biopsy exceeds other methods short of surgery, since 90% of all malignancies can be accurately diagnosed with a false negative rate in most series between 7 and 10% and a false positive rate between 1 and 2%.¹⁻⁵ The procedure works best when there is joint cytopathologic and radiologic cooperation and expertise. In recent years there has been increasing application of pulmonary fine needle aspiration throughout the U.S., not only for the diagnosis of malignancy but also in the evaluation of complex lung disease.

Our experience again re-emphasizes that fine needle aspiration biopsy of the lung is simple, accurate and usually safe and can lead to quicker, less expensive non-invasive diagnoses of benign and malignant lesions.

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Health Care Planning in North Carolina: Migrant Workers Program

Michael F. Fleming, M.D. and Charles S. Hayak, B.S.

OVER 40,000 migrant agricultural workers labor in the fields of North Carolina between May and October each year. There is "almost universal agreement that migrant farmworkers have the lowest health status of any group in the United States."¹ In seven countries where large numbers of migrants work, the prevalence of tuberculosis varies from 12.5 to 64.4 cases per 100,000. The state rate is 17.4 cases per 100,000 population.¹ The infant mortality rate for migrant farmworkers from records at Tri-County Community Health Center (TCCHC), 1982, was 30 deaths per 1,000 live births in contrast to 13.7: 1000 for the state.* This paper presents an overview of the North Carolina migrant health care system.

Dunbar and Kravitz have described migrant farmworkers as "freelance workers who drift from farm to farm, often covering thousands of miles in a month, seeking temporary jobs during the short-lived times of plenty, the cultivating and harvesting times when the crops and the land itself must be served with no time to waste."² This is in contrast to seasonal farmworkers, state residents, who do agricultural work each growing season. There are three major streams where migrant workers follow the agricultural harvest: the West Coast Stream, Midcontinent Stream, and East Coast Stream³ (figure 1).

Every spring approximately 40,000 migrant workers move into North Carolina to work the agricultural fields, cultivating and harvesting tobacco, sweet potatoes and other crops. This temporary and mobile work force supplements the state's 200,000 resident farmworkers, giving the state the largest farmworker population on the East Coast and the fourth largest in the United States.¹ Of North Carolina's one hundred counties, 25 had over 2,000 migrant and seasonal farmworkers in 1980⁴ (figure 2). The migrants who work the fields in North Carolina typically are 50-60% black Americans, 25-30% Mexican Americans, and 15% either Haitians or white.¹

In the migrant farmworker population, serious public health problems normally associated with underdeveloped areas are the rule rather than the exception. Common medical problems seen in migrant populations include tuberculosis, parasites, venereal disease, malnutrition,

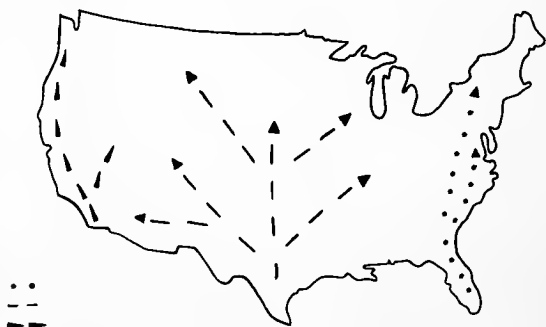


Figure 1. Major streams of migrant travel. The East Coast (●), Midcontinent (---), and West Coast (▶) streams are the three major routes of migrant travel.

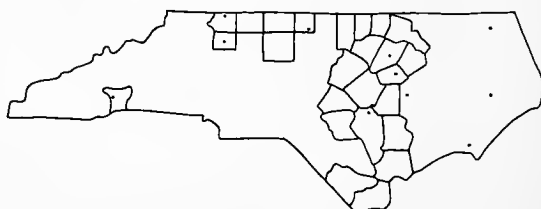


Figure 2. Migrant health programs (●) and counties with high density migrant and seasonal farmworkers, 1980. Twenty-five of the state's 100 counties had more than 2000 migrant and seasonal farmworkers in 1980. Seven of the eleven migrant health programs surveyed are located in these counties.

alcoholism, and violent injuries.⁸ The health problems of this occupational group are tightly interwoven with their culture, environment, and occupation. Poverty, overcrowding, poor housing, poor sanitation, poor education, stress of the camp and work, and chronic exposure to pesticides are daily health risks.

The health care system for migrant farmworkers in the state comprises county health departments, federally funded migrant clinics, local hospitals, and provider physicians. The majority of migrant workers, nationally and in this state, receive their care at county health departments and federally funded migrant health clinics.³ Hospitals also play an important role, providing emergency treatment, inpatient care, and specialty consultation. Obstetrical de-

From the Department of Family Medicine, University of North Carolina, Chapel Hill 27514.

* Watkins EL, Peoples MD, Gates C: Health and social needs of women farmworkers receiving maternity care at a migrant health center. Presented at the 111th Annual Meeting of the American Public Health Association, November 1983, Dallas.

* Grant application program narrative, TCCHC, Newton Grove, NC.

liveries are usually done at local hospitals. Due to economic, communication, and transportation barriers, private physicians are least utilized by migrants for initiation of care. As transient workers, migrants have difficulty qualifying for federal and state assistance programs.³ The state's Migrant Health Program reimburses for physicians at Medicaid rates and hospitals at \$125 per day both for a maximum of three days.*

In North Carolina, migrant health care in counties not served by federal programs is overseen by the Migrant Health Program (MHP) of the Department of Human Resources. The MHP receives state and federal funding for provision of care. In 1981, the Program's budget was \$450,000 (\$251,000 federal). As in other states along the migrant stream, North Carolina's program's funds are mainly utilized through county health departments, some of which operate special migrant programs⁶ (table 1 and figure 2). Only health departments operating special migrant programs record separate data on migrant visits. As mentioned, money is also budgeted for reimbursement to hospitals and private physicians who provide care to migrants. Because of limited funds, priority is given to hospitalizations for deliveries, infants, and children.⁶ The major thrust of the state's migrant health program, then, is handling of acute medical problems rather than prevention of illness. Brown has written that in the migrant health care system, "prevention as a point of view cannot coexist with the pressure of acute clinical activities."⁷

Clinics may offer three types of health care services: ambulatory care clinics for management of acute and chronic illness; preventive medicine programs which include the Supplemental Food Program for Women, Infants, and Children (WIC), family planning, and nutrition counseling; and outreach programs which send health personnel and volunteers into migrant camps where persons are screened for blood pressure, serious illness, and medication needs.

In addition to county health departments, two locally administered migrant health centers receive funding from the federal government's Public Health Service, Department of Health and Human Services, the Office of Migrant Health of the Bureau of Health Care Delivery and Assistance. These centers are the TCCHC in Newton Grove and the Migrant Family Health Service (MFHS) in Hendersonville.

The TCCHC serves Harnett, Johnston, and Sampson counties (1,962 square miles). There are over 200 migrant camps in this area, with an estimated 10,000 migrant workers (one-fourth the state's total). The Employment Security Commission estimates that there are 7,125 seasonal workers in the clinic's catchment area. This clinic is the state's only special migrant clinic that operates full-time year-round. The MFHS serves mainly Henderson, Polk, Burke, Haywood, and Rutherford counties, and migrants from northern South Carolina. This clinic operates only four months each year. As in many migrant clinics, nurse practitioners provide a majority of the care. The TCCHC utilizes two nurse practitioners and one full-time physician while

Table 1
Federal and State Migrant Clinics Surveyed

Federal

Tri-County Community Health Center, Newton Grove
Migrant Family Health Service, Hendersonville

State

Albemarle North (Camden, Currituck, Pasquotank Counties)
Carteret County Health Department
Greene Health Care, Inc. (Greene County)
Hyde County Health Department
Nash County Health Department
Prospect Hill Clinic (Caswell, Alamance Counties)
Surry County Health Department
Wilson County Health Department
Yadkin County Health Department

the MFHS employs three nurse practitioners and one part-time physician.

This paper presents the results of a survey of eleven migrant health care programs in the state. These include the two federally funded migrant health care clinics discussed above and nine health departments or clinics which offer migrant health programs (table 1). The results suggest important factors and programs that should be considered when providing migrant health care.

Methods

A telephone survey of the state's two federally funded migrant clinics and nine clinics (county health departments and one private clinic) that offer special migrant programs was performed (table 1). Data collected include number of migrant outpatient encounters, number of referrals, number of migrants screened by outreach, and number of migrants served at evening clinics during 1982. In addition, the number of referrals that were inpatient hospitalizations, outpatient clinic or specialist referrals, and dental referrals was obtained.

All eleven clinics were able to provide some of the data requested. Five of the eleven clinics were able to give tabulated data. One clinic, Greene, could only provide estimates, with the remainder providing both tabulated and estimated data. Only two clinics (Greene, Prospect Hill) were unable to give tabulated data for the number of outpatient visits. The number of hospitalizations from the TCCHC records includes both referrals directly from the clinic and known hospitalizations of migrants in its catchment area. The MFHS and Greene Health Care clinic could not provide breakdown on referrals. Albemarle, Nash, and Yadkin clinics could only provide a partial breakdown. Six of nine clinics, one federal and five state, performing outreach were able to provide numbers of migrants screened. All five clinics offering evening clinics were able to report numbers served.

Results

Data on outpatient encounters, referrals, outreach, and evening clinics are summarized in table 2. There was a total of 12,003 outpatient encounters reported. The federal clinics served 9,165 or 76.3% of these encounters compared with 2,838 or 23.7% at state clinics. Nash and Carteret

* Personal communication with Ms. Dara Murphy, director Migrant Health Program, N.C. Department of Human Resources.

Table 2
Services Offered and Number of Migrants Served by Federal and State Clinics, 1982

Clinic	Outpatient Encounters		Referrals		Outreach		Evening Clinic	
	#	% of total	#	% of OP	#	% of OP	#	% of OP
Federal								
TCCHC	5,165	43.0	1,636	31.7	4,328	83.8	not offered	
Hendersonville	4,000	33.3	—	—	conducted		160	4.0
Subtotal	9,165	76.3	1,636	>17.9	>4,328	>47.2	160	1.7
State								
Albemarle	322	2.7	74	2.3	475	148	480	149
Carteret	0	0	0	0	not conducted		35	—
Greene Health	50	0.4	—	—	not conducted		not offered	
Hyde	180	1.5	127	70.6	200	111	95	52.8
Nash	0	0	>48	—	>3,500	—	1,011	—
Prospect Hill	950	8.0	27	2.8	1,500	158	not offered	
Surry	74	0.6	78	105	conducted		not offered	
Wilson	840	7.0	442	52.6	500	59.5	not offered	
Yadkin	422	3.5	127	30.1	conducted		not offered	
Subtotal	2,838	23.7	>923	>32.5	>6,175	>218	1,621	57.1
Total	12,003	100	>2,559	>21.3	>10,503	>87.5	1,781	14.8

County programs served migrant outpatients through evening clinics instead of during general clinic hours unless needs were emergent.

Reported referrals were 1,636 from the TCCHC federal clinic, 31.7% of its outpatient encounters, and more than 923 for state clinics, 32.5% of their outpatient encounters. The breakdown of these referrals into inpatient hospitalization, outpatient referral, and dental referrals is shown in table 3. There is a statistically significant difference between federal and state hospitalizations as a percentage of outpatient encounters ($P < 0.001$, Z test for difference of proportions). However, the TCCHC data include all known hospitalizations from its catchment area rather than hospitalizations directly from the clinic alone, thus increasing its reported hospitalizations.

There was no difference between state and federal clinics in outpatient referrals as a percentage of clinic outpatient encounters. The federal and state outpatient referral rates were 18.6% and 18.3%, respectively. The large number of

dental referrals, 309 federal and >143 state, supports other data on the poor dental status of migrants.^{3, 8, 9}

Five of eleven clinics offered evening clinics. Hendersonville served 160 migrants at these, only 4% of its outpatient encounters. On the other hand, the four state clinic evening clinics served more than 1,621 migrants, greater than 57% of total state outpatients. The seven state clinics conducting outreach screened over two times as many migrants than all nine served as outpatients. More than 10,453 migrants were seen by nine outreach programs. The TCCHC performed outreach to 4,328 migrants, 83.8% of its outpatient encounters.

Conclusions

Shenkin has described accessibility as one of four characteristics upon which a health care program should be evaluated.³ Seven of eleven clinics contacted are located in counties with greater than 2,000 migrant and seasonal farmworkers in 1980. The TCCHC alone serves twenty-

Table 3
Breakdown of Referrals

Clinic	Total Referrals		Hospitalizations		Outpatient		Dental	
	#	% of OP	#	% of OP	#	% of OP	#	% of OP
Federal								
TCCHC	1,636	31.7	367*	7.1	962	18.6	309	6.0
State								
Albemarle	74	2.3	7	2.2	—	60	18.6	—
Hyde	127	70.6	6	3.3	99	55.0	22	12.2
Nash	>48	—	48	—	—	—	†	—
Prospect Hill	27	2.8	13	1.4	14	1.5	0	0
Surry	78	105	1	1.4	71	95.9	6	8.1
Wilson	442	52.6	58	6.9	336	40.0	45	5.4
Yadkin	127	30.1	—	57	13.5	—	70	16.6
Subtotal	>923	>32.5	133	4.7	520	18.3	>143	>5.0

* Includes all known migrant hospitalizations from the TCCHC catchment area.

† Approximately 50% of outpatient encounters received a dental referral.

five percent of the state's estimated total migrant population. This theme of location of programs in areas with significant numbers of migrants is also present in the federal Migrant Health Act, which in 1975 began to provide funding for year-round migrant centers in areas with greater than 6,000 migrant and seasonal farmworkers. This was reduced to 4,000 in 1978 due to the rural, low density location of farmworkers. Further extensions of this theme are outreach programs and the suggestion of mobile clinics that travel to migrant camps.³

With a defined migrant service mandate, federal programs can better predict, plan, and utilize their facilities and staff to serve large numbers of migrants. For example, the MFHS is only open during the peak of the growing season. The TCCHC employs additional providers, translators, outreach, and transportation workers during the season. General health clinics, however, serve a broader population, and providing more comprehensive migrant care would be detrimental to other services. Finkelstein has written that "the more comprehensive the program, the greater the risk of underuse of some services, thus threatening the financial solvency of the highly used services."¹⁰ This problem is faced by all clinics serving the general, low density rural population.¹⁰

Outreach programs were offered through nine of the eleven clinics. Personnel from several clinics attempt to visit all the migrant camps in their area. Three of four state clinics screened more migrants by outreach than they served as outpatients. This type of program is a means of screening large numbers of migrants quickly for several diseases, acute and chronic, that are common in a migrant population, including hypertension and tuberculosis. The majority of tuberculosis cases identified at TCCHC in 1982 was through outreach. While the state programs utilize outreach for follow-up visits, transportation arrangement, health education, and screening for acute medical problems, TCCHC also conducts a health questionnaire for chronic illness, review of systems, and blood pressure determinations. The screening, early diagnosis, ability to see large numbers of migrants, and accessibility make outreach a valuable program.

Evening clinics are another means of making care more accessible since they allow migrants to receive care without missing work and pay.^{5, 8} Although only five of the programs offered evening clinics, over 1,781 patients were seen at these clinics. Two of the health departments served migrants solely through evening clinics. It is of note that the TCCHC added evening clinics for the 1983 season, and served approximately 870 persons.

Lastly, the results concerning referrals and referral breakdown suggest several conclusions. The lack of statistical difference between state and federal program outpa-

tient referrals implies that the health status of migrants across the state is fairly homogeneous. It may also imply that services offered by the two types of programs are comparable, especially since the provider staff for both types is similar. However, the federal clinics possess better laboratory and x-ray facilities, and utilize more staff for outreach, translation and transportation. A more detailed investigation of the medical reasons for outpatient referrals would better compare the two types of programs.

Unfortunately, the hospitalization rates that the programs record are different, making comparison difficult. More than 14% of the state referrals were for inpatient hospitalization, 4.7% of their outpatient encounters. The variation in hospitalizations between state clinics themselves, 1.4% to 6.9% of outpatient encounters, and the larger number reported from the TCCHC catchment area point to the importance of local hospitals as a source of care and to differences in local clinic use for conditions requiring hospitalization. Again, further investigation and comparison between the two types of programs are needed.

In conclusion, the most comprehensive migrant programs offer ambulatory care, preventive medicine services, and outreach. Location of programs in migrant dense areas, evening clinics, and outreach improve accessibility of clinic services, allowing for increased care. In addition, outreach is one of the few attempts at early diagnosis and screening in a system of predominantly acute care. While federally supported migrant clinics in high density areas serve large numbers of migrants, only two of these clinics exist in North Carolina. Consequently, most migrants in the state are dependent on health departments and further outpatient referrals for health care. Additional studies to determine reasons for referrals and hospital inpatient use are needed.

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CONTRAINDICATIONS: Nadolol — Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS). Bendroflumethiazide — Anuria, and in those with previous hypersensitivity to bendroflumethiazide or other sulfonamide-derived drugs.

WARNINGS: Nadolol — **Cardiac Failure** — Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well compensated usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. In PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, digitalis and/or give diuretics, and closely observe response or discontinue nadolol (gradually, if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy, exacerbation of angina and, in some cases, myocardial infarction have occurred after abrupt discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1 to 2-week period and carefully monitor the patient. Flusitil® (nadolol) properly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of beta₂ receptors. **Major Surgery** — Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase the risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levaterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents. **Diabetes and Hypoglycemia** — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hypoglycemia, therefore it may be necessary to adjust doses of antidiabetic drugs. **Thyrotoxicosis** — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

Bendroflumethiazide — Use with caution in severe renal disease. In patients with renal disease, azotemia may be precipitated. With impaired renal function, effects of the drug may be cumulative. Use with caution in impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

PRECAUTIONS: General — **Nadolol** — Use with caution in patients with impaired hepatic or renal function (see DOSAGE AND ADMINISTRATION).

Bendroflumethiazide — Use with caution in patients with impaired renal function. Monitor to detect possible electrolyte imbalance. Warning signs of which are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and GI disturbances such as nausea and vomiting. Observe patients for clinical signs of fluid or electrolyte imbalance, namely hyponatremia, hypochloremic alkalosis, hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Drugs such as digitalis may influence serum electrolytes. Hypokalemia may develop, especially with brisk diuresis, in presence of severe cirrhosis. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Response of the heart to toxic effects of digitalis can be exaggerated with hypokalemia. Use potassium supplements such as high potassium foods to avoid or treat hypokalemia. Any chloride deficit is generally mild and usually does not require specific therapy except under extraordinary circumstances (as in liver or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than salt administration except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain thiazide treated patients. Latent diabetes mellitus may become manifest during thiazide therapy. Antihypertensive effects of bendroflumethiazide may be enhanced in the postsympathectomy patient. Careful reappraisal of therapy and consideration given to withholding or stopping diuretic therapy is necessary if rising nonprotein nitrogen or BUN (indicative of progressive renal impairment) occurs. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Thiazides decrease calcium excretion. Pathologic changes in parathyroid gland with hypercalcemia and hypophosphatemia have been occasionally observed with prolonged therapy. Common complications of hyperparathyroidism have not been seen.

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at the first sign or symptom of impending failure. Advise patients of proper course if dose inadvertently missed.

Laboratory Tests — Regularly monitor serum and urine electrolyte levels (see WARNINGS, Bendroflumethiazide, and PRECAUTIONS, General, Bendroflumethiazide).

Drug Interactions — **Nadolol** — When administered concurrently the following drugs may interact with beta-adrenergic blocking agents. **Anesthetics, general** — exaggeration of anesthetic-induced hypotension (see WARNINGS, Nadolol, Major Surgery). **Antidiabetic drugs (oral agents and insulin)** — hypoglycemia or hyperglycemia, adjust antidiabetic drug dosage accordingly (see WARNINGS, Nadolol, Diabetes and Hypoglycemia). **Catecholamine-depleting drugs (e.g., reserpine)** — additive effect, monitor closely for evidence of hypotension and/or excessive bradycardia.

Bendroflumethiazide — When administered concurrently the following drugs may interact with thiazide diuretics. **Alcohol, barbiturates, or narcotics** — may potentiate orthostatic hypotension. **Antidiabetic drugs (oral agents and insulin)** — thiazide-induced hyperglycemia may enhance hypoglycemia. **Other antihypertensive drugs** — additive or potentiated effect. **Corticosteroids, ACTH** — intensified electrolyte depletion, particularly hypokalemia. **Ganglionic or peripheral adrenergic blocking drugs** — potentiated effect. **Preanesthetic and anesthetic agents** — effects may be potentiated, adjust dosage accordingly. **Pressor amines (e.g., norepinephrine)** — possible decrease response but not sufficient to preclude their use. **Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)** — possible increased response.

Drug/Laboratory Test Interactions — Discontinue thiazides before tests for parathyroid function (see PRECAUTIONS, General, Bendroflumethiazide).

Carcinogenesis, Mutagenesis, Impairment of Fertility — **Nadolol** — In 1 to 2 years oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions. **Bendroflumethiazide** — Long-term studies in animals have not been performed.

Pregnancy — **Teratogenic Effects** — **Nadolol** — Category C. In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits, but not in rats or hamsters, at doses 5 to 10 times greater (on a mg/kg basis) than the maximum indicated human dose. No teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women, therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. **Bendroflumethiazide** — Category C. Animal reproduction studies have not been conducted. This drug's effect on the fetus when administered to a pregnant woman or its effect on reproductive capacity is not known. Bendroflumethiazide should be given to a pregnant woman only if clearly needed. **Nonteratogenic Effects** — Since thiazides cross the placental barrier and appear in cord blood, weigh anticipated benefit of the drug in pregnant women against possible hazards to the fetus, these hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other reactions which have occurred in adults.

Nursing Mothers — Both nadolol and bendroflumethiazide are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants either discontinue nursing or discontinue therapy, taking into account the importance of CORZIDE (Nadolol-Bendroflumethiazide Tablets) to the mother.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Nadolol — Most adverse effects have been mild and transient and have occurred in approximately 10% of patients. **Cardiovascular** — Bradycardia with heart rates of less than 60 beats per minute occurs commonly and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or lightheadedness reported in approximately 2 of 100 patients, paresthesias, sedation, and change in behavior reported in approximately 6 of 100 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash, pruritus, headache, dry mouth, eyes, or skin, impotence or decreased libido, facial swelling, weight gain, slurred speech, cough, nasal stuffiness, sweating, tinnitus, blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with praloxolol has not been reported with nadolol. The following adverse reactions may also occur: **Central Nervous System** — reversible mental depression progressing to cataplexy, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation in time and place and short-term memory loss, emotional lability with slightly clouded sensorium, decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis, ischemic colitis. **Hematologic** — agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat, lymphadenitis, respiratory distress. **Miscellaneous** — reversible alopecia. **Peyronie's disease**, erythematous rash, arthralgia/synovitis.

Bendroflumethiazide — **Gastrointestinal System** — anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis. **Central Nervous System** — dizziness, vertigo, paresthesia, headache, xanthopsia. **Hematologic** — leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia. **Dermatologic-Hypersensitivity** — purpura photosensitivity, rash, urticaria, necrotizing angitis (vasculitis, cutaneous vasculitis). **Cardiovascular** — orthostatic hypotension may occur. **Other** — hyperglycemia, glycosuria, occasional metabolic acidosis in diabetics, hyperuricemia, allergic glomerulonephritis, muscle spasm, weakness, restlessness. Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

OVERDOSAGE: Nadolol may cause excessive bradycardia, cardiac failure, hypotension, or bronchospasm. Overdosage of thiazides may cause lethargy, which may progress to coma within a few hours, with minimal depression of respiration and cardiovascular function and without evidence of serum electrolyte changes or dehydration. Gastrointestinal irritation and hypermolemia may occur. Transitory increase in BUN and serum electrolyte changes may occur, especially in patients with renal impairment.

Treatment — Nadolol can be removed from the general circulation by hemodialysis. In determining duration of corrective therapy, take note of the long duration of the effect of nadolol. In addition to gastric lavage, administer the following measures, as appropriate: **Excessive Bradycardia** — Administer atropine (0.25 to 1 mg). If there is no response to vagal blockade administer isoproterenol cautiously. **Cardiac Failure** — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation. **Hypotension** — Administer vasopressors, e.g., epinephrine or levaterenol. (There is evidence that epinephrine may be the drug of choice.) **Bronchospasm** — Administer a beta₂-stimulating agent and/or a theophylline derivative. **Stupor or Coma** — Supportive therapy as warranted. **Guinea Pig** — Institute supportive measures as required to maintain hydration, electrolyte balance, respiration and cardiovascular and renal function.

DOSAGE AND ADMINISTRATION: DOSAGE MUST BE INDIVIDUALIZED. Patients with renal failure require adjustment in dosing interval, see package insert for dosage in these patients.

Consult package insert before prescribing CORZIDE (Nadolol-Bendroflumethiazide Tablets).

HOW SUPPLIED: Available as scored tablets containing 40 mg nadolol combined with 5 mg bendroflumethiazide and 80 mg nadolol combined with 5 mg bendroflumethiazide in bottles of 100.

Meet George Moore, Your New Executive Director

Patricia K. Hodgson

MEET George Moore. He's the new Executive Director of the North Carolina Medical Society, after a fast five month learning period as Associate Executive Director.

George Moore is a native North Carolinian, born in the small community of Pilot, "a state of mind which is close enough to Zebulon that they understand each other." He is a product of three of the State's major universities, having attended NC State, graduated with a degree in English from UNC, done graduate work in public administration and business administration, and started his first job at Duke.

That first job was an unusual one, particularly for someone just out of college. Soon after the Russians launched Sputnik I in the late 1950s, there was considerable concern in many circles in this country because America had not put up the first space satellite. Most people agreed that the nation's educational system was the primary culprit for our having fallen behind Russia in the sciences.

On the campus of Duke University was the Army Research Office, an administrative unit of the Chief of Research and Development of the Army. The Office placed research contracts, mostly with educational institutions throughout the country, and it was heavily involved in the mammoth catch-up effort in space exploration. Because of that work, the Army Research Office had excellent lines of communication with most major colleges and universities. It was the catalyst in the creation of a program designed to help produce the scientists, engineers and mathematicians the nation needed immediately and in years to come.

Enter George Moore, recent college graduate: "They hit on this notion that maybe what we ought to do is identify the really first rate minds among the high school kids in this state and expose them to bench scientists, give them some hands-on scientific experience, do some seminars, and show them what a career in science would be like." With the help of the Department of Public Instruction, the Academy of Science, and the major high schools in the state, about 350 youngsters were identified, invited to take part in the program, and spread out among the three universities in the Research Triangle area since there were too many for any one campus. Moore directed the program, the Junior Science and Humanities Symposium, from Duke and it was an enormous success for both the students and the faculty. The word shortly got out to other states, and the program grew. From the single pilot program in the early

60s there eventually evolved a network of 25 regional centers at major universities across the country before Moore left. The culmination was a national symposium to which the brightest of the bright were invited. This was held at the U. S. Military Academy at West Point, co-sponsored by the United Nations and Princeton University, and among the speakers were Werner Von Braun, J. Robert Oppenheimer, and Edward Teller.

This job gave Moore exposure to almost constant travel, to the major scientific institutions, to federal agencies, to the U. S. Office of Education, to business and industry, to the generals of the Army, and to the leading scientific researchers in the country. He was lured away from that position by one of the members of the Program's Advisory Council who suggested to the Superintendent of Schools in Roanoke, Virginia that Moore might be the right person to direct the Federal programs for that school system.

Because of recent Federal mandates, there was an abundance of money available for new, innovative programs in the public schools. Moore became head of the Federal programs for the Roanoke schools: "I saw an opportunity to do some things I hadn't done at Duke. I was ready to start broadening my horizons a little bit."

The first thing they did was develop a model kindergarten program. There were no certified kindergarten teachers, the classrooms were physically inadequate for kindergarten-aged children, and there was next to no information about how to start a good kindergarten program, but they forged ahead anyway, and they succeeded. With about \$500,000 in federal funds they developed certification methods, renovated school rooms, developed materials, and became the model for the state in the process.

Another interest gaining prominence at that time was the other end of the age spectrum, the undereducated adult. The Roanoke schools developed an adult basic education program during Moore's tenure there that became the model for other such programs throughout the country. A third program with which Moore was involved and of which he is very proud was the Head Start Program, which was another great success. "All in all, we had ourselves a very nice time."

Roanoke lasted about three years, and then Hollins College came calling. The reason Hollins College came calling was the Dean of Hollins, who served on the School Board in Roanoke, and came to know Moore through School



Board meetings. When Hollins found that it needed a new head of its external affairs program it came to Moore, and he went to Hollins. His responsibilities included development, alumnae relations, publications, press relations, governmental relations, and a multi-million dollar capital campaign that was just in the planning stage. "I'd never done any of this sort of thing for higher education and it seemed like one of those things that I'd like to do."

When Moore took the position at Hollins the endowment was \$3 million; when he left 12 years later, it was \$22 million with another \$3 million in pledges. Many new facilities were constructed and many of the fine old buildings, most of which were placed in the National Register of Historic Places, were refurbished.

"The only thing that could have taken me away from Hollins was an opportunity to come back home to Raleigh. North Carolina State was looking for an Associate Vice Chancellor to do essentially what I'd been doing at Hollins. I thought about it a good while and finally decided that it was something I'd like to do."

Moore took the NC State position in 1980 and found himself facing a large and unfamiliar bureaucracy, "which took some getting used to." The fact that State is the research institution of the University system in North Carolina and the fact that State provides the trained manpower needed by North Carolina's many technology-based industries make it a particularly attractive investment for corporate philanthropy in the 1980s. Businesses invest their

dollars in financial aid, in research equipment, and in faculty development in an effort to keep the finest teaching and learning minds at State teaching and learning.

Unlike many universities, which have a centralized fund-raising structure for the entire institution, NC State has fourteen separate foundations, each chartered and incorporated and each raising funds for its own constituency. Moore's job was to coordinate the efforts of these foundations, to discover new sources of support, to guide solicitation efforts of all constituents to the most appropriate foundation, to make friends for the University throughout the state.

With a career in education from Head Start to university, what brought Moore to the North Carolina Medical Society? "Except for the medical science aspects and the issues of organized medicine, the activities and services provided to our membership are essentially the same in nature as those services provided to alumni." Many facets of NCMS organization are very similar to the services of other organizations: "administration is administration, organization is organization. I don't find the day-to-day activities of the Society in terms of working with the staff and working with the leadership very different from what I've always done."

But what is different? "What I do have to learn — and there is so much of it to learn — is the medical issues, the concerns of organized medicine. Those are issues that will take me a long time to be knowledgeable about. I've already learned a lot. I have a good bit of information, but information is not knowledge. Only when you can learn to use all those bits and pieces of information with some perspective does it become knowledge, and that's what I'm short of. Those issues and their implications are so much broader and deeper than I'd ever imagined them to be."

One of Moore's high priorities, which should be in place by the time you read this, is the recently created Committee on Goals and Objectives which he views as a major step forward for the Society: "I hope what will come from this is a blueprint of where we want to go over the next five year period. It will identify and address the major issues of the Society and then set out to establish some specific goals and objectives about how we handle these issues, what we should be doing, and exactly how we're going to do it. This has implications for the use of our resources, both human and financial; it will guide our budgeting process and allow us to develop realistic budget projections; and it will determine the personnel that we need and what those people will be doing in their day-to-day jobs for the Society. I really don't think we can do a workmanlike job in service to the members until we have in place that sort of blueprint."

Another high priority with Moore is membership development. "With the data provided by the recent member and non-member surveys, we have a useful source document to build on our strengths and shore up our deficiencies. We have a good notion of how we are perceived, and we can use that information to make membership in the Society more attractive. We've got to show that the product we offer is useful and worth far more than the price of membership. I hope that an intensive membership campaign is just ahead, that members will be calling on non-members to present our case and to show the importance of many voices speaking as one. We need to concentrate



especially on the younger physicians to suggest to them the importance of their role in organized medicine."

Here are some of George Moore's early thoughts on matters of concern to the North Carolina Medical Society.

- On medicine today: "Never has medicine been faced with as many serious concerns, some of which could change the way a physician practices medicine: the increasing intervention of government; the terrible concerns about escalating costs; the different ways of providing health care — the settings and the organizational systems — that are coming along that are at heart an effort to reduce the costs of health care but which may pay too little attention to the quality of care."

- On the role of businesses in the changing practice of medicine: "It's costing them an inordinate part of their resources to provide employee health care benefits. Obviously they're looking for ways to reduce their costs or at least minimize them without withholding from their employees the medical benefits that they've been entrusted

to give. But these are corporate resources that will be deployed like all other resources — where they will return the greatest benefit per dollar spent: in outpatient settings, in free standing units of various sorts, with built-in financial disincentives such as co-payments, less first dollar coverage, and the like. There will be groups of physicians working together in HMOs and IPAs and Preferred Provider Organizations in ways that we couldn't even anticipate a few years ago."

- On Medicare: "The Medicare program and the government's concern about those rising costs are likely to have an impact beyond Medicare. As experience shows how well the DRGs and the peer review process will work, then I think it's only one small step from there to the adoption of these same sorts of programs by the commercial insurers."

- On the role of the North Carolina Medical Society staff: "I think the staff of the Society has to be more of a motivating force than it's ever been in the past. We've got to be seen by our membership as people who are in possession of the facts. We must have the information they need and we must see that they get that information. We've got to be more alert to opportunities to help physicians as they serve their profession through our Society, as they are wrestling with the various issues that arise. We must be mindful always that because we're hired full time to provide services, we must in many instances know more about a particular issue than the individual physician could possibly have time to know. We've got to find ways to help that physician understand the issues. We've got to anticipate needs. I want us to be a professional group that is perceived by its member physicians as just that. We have to earn that. I think too often in a membership organization the staff is reactive; they don't tend to move on matters until they get requests to do so. Clearly, policy decisions remain the prerogative of the membership, but in the day-to-day operation the staff really has to be proactive, and that is essentially what I want us to be."

"We've got here the makings of a very good staff. We must among ourselves be very proud of what we do and how we do it. I really hope that among the staff within a short time there will be the feeling that we are the very best state medical society in the country, and there's no reason why we can't be."

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The Doctor Glut

Eugene W. Linfors, M.D., editor

Dr. John Gamble of Lincolnton has encouraged us to establish a forum for communication among North Carolina doctors. This month we begin the Physicians' Forum. The members of the forum to discuss each issue will be selected by Eugene W. Linfors, M.D., who is a member of the General Medicine Division of Duke. We welcome your letters to the editor to give your opinion of both the issue of the month and the views of the doctors constituting the forum.

The question for the June issue is: From your own experience, are we educating too many doctors? If so, what should be done and how? Remember, there are three primary sources of doctors: American and Canadian schools, foreign schools, and schools for American citizens established in the Caribbean. Many foreign trained doctors circumvent immigration quotas by marrying U.S. citizens.

This new feature does not replace our regular Letters to the Editor column.

Eugene A. Stead, Jr., M.D.

From Dr. Eben Alexander, Jr., a neurosurgeon in Winston-Salem.

Demographic studies clearly point out that there will be far more physicians in 1990 per capita than there were in 1970. Physician and public surveys indicate that while physicians in general feel we have enough or possibly more physicians than we need, the public is not yet so sure of this. There are some geographical areas in which the public wants more physicians, and there are some specialties in which there are not enough physicians, but these latter are isolated and uncommon.

If the perception of a surplus is based on the situation in 1960, for example, then there is a "doctor glut." But the perception of a surplus is a relative matter, and there are a number of factors that will alter the present situation:

1) There will be 5,000,000 more persons over 65 years of age by 1990, and there will be a 75% increase in persons over 75 years of age by the year 2000. Since 1950, the number of persons older than 65 years has increased 106%, and there are more persons now alive over the age of 65 than all the persons world-wide who have lived to that age in the past.

Geriatric patients require more hospitalizations than patients younger than 65 years, and require them for longer periods of time; they also have more operative procedures. Geriatrics is a specialty that will need more physicians.

2) There are far more valid, effective therapeutic drugs and methods for treatment than were available 30 years ago, although many persons are still not being treated adequately with those drugs. In 1950, there were no effective drugs for hypertension; now there are scores of these drugs for various types of hypertension. When more patients need better treatment, more physicians in all fields are needed.

3) It is not likely that the physicians of the 1990s will want to work the 70- to 80-hour weeks and long week-ends their predecessors did. The new physician is surrounded by the 40-hour week, by every third week-end on duty, and by all the usual habits of his or her friends, and such habits will rub off.

4) Many more physicians will be involved in administration and industrial positions than at present.

The young woman and young man who want to study medicine today should have the same opportunities their predecessors had 30 to 40 years ago. If those already in practice perceive that there are enough or too many physicians, they still have no justification for denying access to their profession by as many young persons as want to consider a medical career. And who can predict with certainty what the needs will be 20 years from now?

The practicing neurosurgeons of the United States, represented by the Joint Socio-Economic Committee of the American Association of Neurological Surgeons and the Congress of Neurological Surgeons have repeatedly stated that there are too many neurosurgeons and that we should cut back on the number of neurosurgical residencies in this country. They have called on the American Association of Neurological Surgeons to cut back on that number. This is simply one example of a small specialty that is seeking to have control from above.

Other groups have implored the AMA to "do something about the surplus of physicians." Some physicians who know little of the legal aspects of accreditation consider the Liaison Committee on Medical Education to be the proper agency through which to cut down on the number of persons being admitted to medical school.

It is well to remember that we have had a large increase in the number of 22-year-old college graduates since 1965. The number of applicants to medical schools of the United States has closely paralleled that number of 22-year-old graduates for the past 55 years. If there had been fewer openings in medical schools over those years, more American college graduates would have had to seek medical training abroad. Now, however, the number of 22-year-old college graduates is declining, and the cost of an education is increasing, not only for the student but for the governing institutions — in many instances, the governing institutions being the individual states. The state legislators hear from the GMENAC (Graduate Medical Education National Advisory Committee) report that we have or will have too many physicians and they find themselves under pressure from their constituents and fellow legislators to save precious tax dollars by decreasing (or at least not increasing) the support to state medical schools.

The number of graduates of medical schools in America will almost certainly diminish, since no new schools are in formation, and many schools have already reduced the size of their entering classes. With the drop in the number of 22-year-old graduates, state schools that largely limit their admissions to students from that state are finding a smaller and sometimes less well-qualified pool of applicants.

The American Medical Association, the Association of American Medical Colleges, the Liaison Committee on Medical Education or even a specialty organization such as the American Association of Neurological Surgeons — none of these or similar organizations can determine the number of graduates from medical school or the number of physicians being trained in their specialty except on the basis of quality, which must always be justified.

Rather, the market place and the judgment of individual students in deciding on a medical career should best decide how many first-year medical students we have. States will decide on the number of students to be admitted to the schools they support, depending on the number of physicians needed and the funds available.

As for the students who choose to go abroad for their training in medicine, there can be no control over their numbers except by the State Department, possibly by the General Accounting Office, or by some other Federal Agency. But for their return to obtain graduate training and licensure here, there will be control on the basis of quality by the Accreditation Council on Graduate Medical Education and on the basis of law by the State Boards of Medical Examiners. The Federation of State Medical Boards has made strenuous efforts to obtain information about foreign medical schools to aid the individual state boards of medical examiners in making the appropriate decisions. This is a sincere effort to maintain the quality and high standard of medical practice in America, and is a better means of controlling the "doctor glut" than trying to limit the number of persons obtaining a medical degree because those in practice perceive we have too many.

N. B. The already-employed taxi drivers in San Francisco recently launched a horn-blowing protest before the Mayor's office to keep her from issuing additional licenses to drive cabs in preparation for the Democratic National Convention in July '84. Similar??

From Dr. W. G. Anlyan, Chancellor for Health Affairs in Durham.

It is a three layered problem: 1) American and Canadian schools; 2) USFMGs educated in the Caribbean and elsewhere abroad; 3) alien FMGs, particularly those from developing nations.

Regarding layer #1, I believe we have overbuilt the number and size of American medical schools. I cannot comment on the Canadian schools since presumably they serve primarily the needs of Canada. Layer #2 is uncontrolled since they are not accredited by the liaison committee on medical education. We don't know the exact size of the pool. The quality varies from diploma mills to more organized medical schools. If left to individual states to license these graduates, there is no question that states like New York will be more lenient not only because of the needs of their governmental and municipal hospitals, but also because the political clout of the parents of the students is tremendous. As a matter of fact, I learned in New York recently that Governor Cuomo had as one of his top priorities to build a medical school in Queens. It was a political pledge. He will undoubtedly absorb most of the class from Granada. It is probable that the City University of New York will be charged with running it. Layer #3, to put a quota on the admission of alien FMGs, has been suggested by GMENAC. The federal legislation which was submitted was defeated by states such as New York.

The only possible combination of solutions would be as follows:

- A. For the U.S. medical schools to cut back on their enrollment on a voluntary basis rather than by a federal edict.
- B. To require one or two years of an approved residency training program on a national basis as a prerequisite to obtaining licensure in all 50 states.

Keep in mind that the physicians entering practice in 1984 will on the average have graduated from medical school in 1976 before the development of the major bulge in enrollment. The big bulge is yet to come and will probably hit in the period between 1990 and the year 2000.

From Dr. George W. Crane, Jr., a dermatologist in Durham.

Is there a doctor glut? In the rural areas, no; in the urban areas, yes.

Durham County General Hospital has 462 beds available at this time, and lists 240 physicians on the medical staff, roughly 2 patients per doctor.

Many nondermatologists are treating dermatologic problems due to competition for patients, or because they feel comfortable dealing with them after a brief course or preceptorship in dermatology.

Duke and University of North Carolina each has 3 residents completing the dermatology program every year and many establish practices in this and the surrounding areas.

In the past 7 years the above factors have reduced our patient load to the point that two dermatologists can handle a practice that formerly required 3.

Evening and Saturday office hours are once again available in some private practices.

Suggested methods to correct surplus:

Medical school enrollment reduction: State and county medical societies may be required to urge state and Federal legislatures to stop spending tax money to subsidize the medical schools on a per student basis. With the exception of a few schools, such as Duke, this move is unlikely to be initiated by the school due to a loss of income.

Limit the number of Americans who train in foreign medical schools and return to the United States to practice.

Foreign-born, foreign-trained physicians taking post-graduate training in the United States should return to their home country or have legal restrictions on licensure even if they marry an American, or have children born in the United States.

From Dr. John R. Gamble, Jr., a general surgeon in Lincolnton.

As a practitioner in an average rural North Carolina county I have not experienced a doctor glut. I know that we will continue to need replacement physicians, new physicians to meet population and increasing utilization needs, and new physicians with specialty and sub-specialty skills. Our county population has increased forty to fifty percent in the past twenty years and our physician population has more than doubled and we are actively recruiting physicians. I feel that any patient who feels the immediate need of physician care should have access to that level of care and that a patient who seeks an appointment should find one available in no less than three or four days.

Should others disagree on the doctor glut I feel that the key point is not to over react and cut back on the educational opportunities of our state's own citizens and thus continue the influx of foreign national physicians. Organized medicine must get its facts and plans organized to insist that the United States Immigration Service not continue its policies of bringing in foreign physicians as a detriment to the opportunities of our state's citizens. I personally feel that our state and other states have the obligation to provide the educational opportunities to their own young people and thus fulfill the expectations to which they are entitled and not default on this responsibility by allowing career openings to be filled by physicians from other countries.

From Dr. G. Radford Moeller, an internist in Pollocksville.

In 1969, as I contemplated a career in medicine, a wave of opinion was cresting in this country which contended that a significant shortage of doctors existed in America. Some individuals even purported to say that a "crisis situation" existed. Others were skeptical, stating that no shortage existed and that a redistribution of physicians could rectify the perceived short fall of health care providers.

In 1973, when I entered medical school at Duke, I discovered that the size of my class was significantly greater than preceding classes. This fact seemed to validate the concept of the "doctor shortage."

In 1982, however, as I eagerly sought a challenging position as a Rheumatologist in private practice, I discovered that an amazing proliferation of sophisticated, subspecialty medicine had quietly occurred in North Carolina.

Cities which had no Rheumatologists when I began my fellowship had, in many cases, more than one by 1982.

At Craven County Hospital in New Bern, there were but approximately 25 physicians in 1970. Today there are in excess of 100. Yet during that same period, the population of Craven County increased less than 10%. I know of no physician at our hospital who feels underutilized. How can a stable population support such a dramatic increase in the size of a medical staff?

I believe that just as NMR and CT scanners have failed to replace older, more traditional, diagnostic tests, the arrival of subspecialists in the many disciplines of medicine previously not represented in our community has provided talents which, in most cases, do not directly duplicate those of the existing physicians. In this sense, then, there is no "doctor glut" in New Bern in 1984

However, there obviously is an end point past which such phenomenal growth will result in an underutilization of physicians. I believe that as New Bern and most towns in North Carolina rapidly reach a condition in which virtually all subspecialties of medicine are represented, a necessary reduction in the rate of growth of the physician pool will have to be instituted. If this does not occur, the "doctor glut" created will surely impose a counterproductive, overly competitive practice environment, which I believe will both increase the total cost of delivering quality health care to our patients and serve to undermine many of the moral imperatives that have to date directed our practice of medicine.

I believe that steps must be taken to avoid a needless, wasteful "doctor glut." Medical schools should be induced to reduce the size of their entering class to original pre-"doctor shortage" levels. The ease with which certain Americans, unsuccessful in their attempts to gain admission to American medical schools, are able to return to practice in North Carolina after obtaining the MD degree (often in the Caribbean and Mexico) needs reevaluation. Steps should be taken to ensure that foreign graduates of foreign medical schools who seek subspecialty training in the United States, often unavailable in their home country, are encouraged to return to their native countries — thus providing for the intended dissemination of medical techniques and knowledge.

I suspect that any attempt by a physician organization to encourage and implement such maneuvers will be viewed as a monopolistic giant attempting to protect its self-serving interests. Medicine has no shortage of biased critics today. Therefore I would advocate that the burden of implementing these measures should fall correctly upon those who, among others, argued so forcefully in favor of an expansion of the physician supply in the 1960s, the State and United States legislatures.

In 1984, in Pensacola, Florida, physicians solicit patients through the use of roadside billboards and immodest telephone yellow page advertising. These outward evidences of the "doctor glut" there only allude to other dramatic, negative departures from the traditional style and code of medical practice fostered by the unfortunate influences of excessive competition. I believe the rate of growth of the physician pool in North Carolina must be reduced if we are to avoid the "doctor glut" and its detrimental

consequences for both our patients and ourselves.

From Dr. John W. Watson, a family practitioner in Oxford.

The doctor glut has not yet arrived in Granville County or in any other rural county, I suspect. If one were to ask this question of my fellow physicians, the answers would vary depending on the physician and his specialty. For example, surgeons do not feel that there is a need for more surgeons but do think there is probably room for more internists and family practitioners; conversely, internists and family practitioners might disagree with the notion that more of themselves are needed.

When I came to Granville County almost 30 years ago, there were 19 physicians none of whom were board certified in any specialty except the radiologist whom we shared with three other communities. The surgery, obstetrics, anesthesia, and general medicine were all performed by general practitioners. The emergency rooms of two hospitals, one black and one white, were covered full time by these physicians. There were approximately 120 beds total in the two hospitals whereas today there is one hospital with 62 beds. Included in those 19 physicians were two black physicians. There were no female physicians and no graduates of foreign medical schools.

Today we have 14 full time doctors of whom eight are now in family practice and most board-certified; there are two internists, one board-certified and one board-eligible; there are two board-certified general surgeons, one board-certified gynecologist, one board-certified radiologist, and one board-eligible psychiatrist. In addition, there is a urologist shared with another community, a rural health clinic with a family nurse practitioner and physician's assistant, and an office that three out-of-county physicians staff which is equal to one full-time physician. There is also approximately three-fourths coverage of our emergency room contracted with an emergency room service.

The physician population today has other differences from that of 30 years ago. Two of our current doctors are

United States citizens who graduated from foreign medical schools. Two more are immigrants who are graduates of foreign medical schools, and our shared urologist is also an immigrant who was educated abroad. We have one black full-time physician, and three physicians sharing one office on a part-time basis are black. We also, last but not least, have one female physician, a psychiatrist.

The population base from which our patients are drawn has decreased somewhat over the past 30 years although the total county population has increased. There are a variety of reasons for this, mostly related to geography, to improved highways, and to the improved technology in medical care.

We now have approximately the same physician-to-patient ratio that we did 30 years ago; however, our make-up is entirely different and we offer more services. The years in between now and 30 years ago were sometimes very difficult with only seven or eight full-time physicians covering emergency rooms, delivering babies, and generally staying full-time fatigued.

No, there is not glut of doctors in Granville County now. In the event such a glut should develop, which I feel is unlikely, the only recourse would be for medical schools to cut class sizes and/or for states with many schools to consolidate them. Two factors will work against a glut of physicians in active practice. The medical schools have increased the percentage of female students to 30-40% of their class. It is probable that many of these physicians will at least have periods in their professional lives when they will not be in active practice or only in part-time practice similar to what has happened with registered nurses. Another factor is that of earlier retirement for physicians. In the past, physicians have pretty much died with their boots on; however, with a more plentiful supply of physicians, they are more likely to retire earlier, particularly if they are able to sell their practices while they are still flourishing.

If a glut of physicians does develop, then I believe that the practice of medicine will change drastically with all sorts of entrepreneurs becoming involved in medical care and all of us will suffer — patients and physicians.

- **EDITOR'S NOTE:** I am delighted by the response to our first question of the month. Thank you for your opinions.

Health manpower needs and the "doctor glut" are extremely important issues. Obviously there are many different currents of thought concerning whether or not the problem exists and, if so, what to do about it. The responses in this issue of the *Journal* illustrate some of these currents.

Two recent articles in *The New York Times* also illustrate some of the controversy. In an article published on April 4, Ronald Sullivan reported that the New York State Health Department would begin to enforce a law barring American students enrolled in "unapproved" foreign medical schools from completing their medical education in New York State teaching hospitals. (In 1981 the State Board of Regents in New York had set up a system of inspecting and approving off-shore schools.) In a later article (April 18) the same reporter stated that another medical school would soon be opening in New York City to graduate more black and Hispanic physicians.

North Carolina Medical Journal

Features for Patients

June 1984

Stepped Care for Diabetes Mellitus

Geo. J. Ellis, M.D.

This article is pure opinion, with no data to confuse anyone. It may be useful for people with diabetes trying to decide just how they would like to structure their medical care, and for physicians and other health care providers trying to evolve more effective ways of dealing with diabetes mellitus — a common condition that requires a different approach from most others. It is the viewpoint of a consultant seeing patients who want better diabetes management and who are seeking a specialist with the hope that he can help them. If you have diabetes, you may see the condition as resembling a 50% surcharge on your tax bill (and if you don't pay it, we'll kill you!). It's simply unfair for you to be selected by the gods to have diabetes. You may have a variety of feelings about it, such as anger, sadness, or frustration; but what you do about it is up to you. If those feelings keep you from caring for yourself as you feel you should, tell your doctor. S/he may be able to help you talk through those feelings or arrange for counselling if additional help is needed.

What is diabetes?

What you are dealing with is an inherited or acquired defect in insulin

secretion or action. Lack of insulin effect means glucose cannot enter cells efficiently, causing blood sugar levels to rise — often to the point that the kidney can no longer salvage all the filtered sugar — and you waste sugar, water to dissolve it, and minerals into the urine. When control is very poor, high sugar levels can draw water from the brain and impair consciousness. By this point, body cells are starved for the energy normally provided by glucose (the major blood sugar). The energy shortage is helped by breaking down fat into small particles (short chain fatty acids and ketones). More small fragments are made than the body can burn. This excessive production may

lead to *diabetic acidosis*, a life-threatening emergency.

With treatment, diabetes can be controlled, but often not perfectly. It's easiest to balance diet, exercise, and insulin well enough to avoid ketoacidosis and coma. But even modest elevations in blood sugar over many years are thought to increase the risk of long term complications of diabetes such as blindness, painful nerve damage, and kidney failure. We have increasingly clear notions of how elevated blood sugars may be linked to the chronic complications. We now believe that even these complications may be avoided or minimized — in some who seem luckily protected from developing them, and



From the Division of Endocrinology and Metabolism, 2924 Duke Hospital, Durham 27710.
Illustrations by Ernest Croige, M.D.

in others — by maintaining very precise control of blood sugar to near normal levels. It seems best always to have normal blood sugars, but any improvement, even after years of poor control, may lower future risks.

Control Strategies

Control may be achieved by a series of strategies that may have a small to intolerably great impact on your life style. Most important is a meal plan, composed of a balanced and wholesome variety of foods. Meats and other foods are chosen to moderate cholesterol and saturated fat intake. Breads and vegetables that contain complex carbohydrates and that are rich in fiber are best to smooth the fluctuations in blood glucose. Meal planning using "ex-

changes" of composable foods encourages variety and flexibility while maintaining a stable caloric intake and an even distribution of fat, carbohydrate and protein. Rapidly absorbed simple sugars are minimized. Three to six feedings daily help spread food absorption to match needs and insulin effect. This amounts to the sort of diet an early settler in this area might have chosen spontaneously, but for a generation used to convenience and junk foods, the change can be a shock! Regular exercise is important in achieving full insulin effectiveness. It may be as simple as walking one to five miles daily, or you may seek additional benefits from more vigorous "conditioning" levels of exercise like jogging or bicycling.

When these measures fail to achieve normal blood glucose, agents to lower blood sugar may be prescribed. Those who can make *part* of their insulin requirement may respond to pills which may help the body to produce more insulin and/or make the available insulin work better. Others may require replacement of insulin, which must be injected at least daily. Unlike some medications, which are optimally distributed by the body with infrequent doses, insulin is difficult to deliver with the proper timing. Normally, insulin increases in the blood after each feeding, and — to avoid low sugars (hypoglycemia) — should fall to lower levels during exercise and before feedings. Such reductions in insulin levels are impossible to achieve with

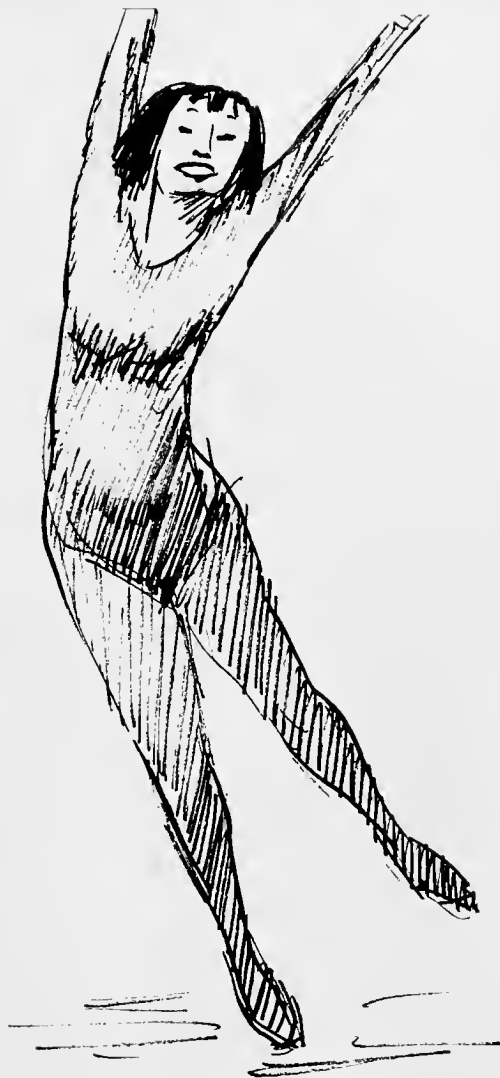
... a generation
used to convenience
and junk foods ...



a single daily injection of insulin when the patient is unable to produce any insulin. If the insulin dose is then increased until some "target" blood sugar (commonly before breakfast) is normal, there is often excessive insulin at other times — especially during the night. This causes low blood sugar (hypoglycemia) which may be felt as unpleasant hunger, sweating, tremor, and rapid heart beat. In severe "insulin reactions" there is a risk of seizures, unconsciousness, brain damage, and even death. When optimal control follows a single daily injection of insulin, it is because the patient, once provided enough "basal" insulin to lower fasting blood glucose to normal, is able to produce enough short acting insulin to match feedings. Others may require two to four injections or even a pump to match insulin levels to the body's needs.

Which doctors can help?

Chasing how to manage your diabetes — and what doctor to advise you — is difficult. You should consider your goals. Do you simply want to expend the least energy to stay out of the hospital? Will you do *anything* to preserve your health? Review your resources for dealing with diabetes, including time, ability to learn, support for expenses, and help from your family. In any case, most will begin with a primary care physician, usually a family physician, pediatrician, or internist, and often the doctor who helped you establish the diagnosis of diabetes. The time to consider consultation is when you and your physician are unable to achieve the control you desire despite your best efforts. A consultant in diabetes may well be trained in greater depth with respect to diabetes than your primary physician. However, s/he will generally maintain this expertise at the expense of general medical knowledge. So it may be wise to rely on your primary physician to support your diabetes program and to deal with other problems even while you are seeing a specialist about your di-



regular exercise is important

abetes. This arrangement, consultative management, may prove both safer and more economical for you. When your diabetes control has reached the optimal level, you may be able to maintain it with the assistance of your primary physician, using your consulting specialist for unusual problems as needed.

New Roles for You and Your Doctor

Your role in managing diabetes is different from your role in other more acute health problems. Rather than simply follow a routine prescribed by your doctor, it may be best for you to take over the day to day adjustments required for optimal control. You

THERAPY education returns to the familiar triad of diet, exercise, and hypoglycemic therapy. Your meal plan prescription is optimally designed to achieve and maintain ideal weight and to minimize swings in blood glucose during the day. There may be special recommendations regarding fat content and sodium or

Figures 1 and 2 are an abbreviated outline of possible elements of a

Figure 1. Side 1 of the Duke Diabetes Education Checklist.

from storage on blood proteins, increasing their glucose-lowering effect. Hypoglycemia caused by oral agents may last several days and often warrants hospitalization. It is wise to ask your doctor and pharmacist about such potential drug interactions whenever you are prescribed a new medication. Such hypoglycemia may also follow use of over-the-counter medications (especially those containing aspirin), so check these out as well. The greatest advantage is that a few patients can achieve continuously normal blood glucose control much more easily than they could with injected insulin; this is because

We instruct most patients in using injectable insulin, even when they may not require it daily. During an illness, insulin requirements may rise so that a purified insulin must be used temporarily to maintain control. Maintaining control during illness helps you to heal more effectively, prevents symptoms from the diabetes itself, and reduces the risk of "islet cell decompensation," or impairment

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of the ability to produce insulin caused by very high blood sugars continuously stimulating the pancreatic islets. Because of the "dead space" in syringes with detachable needles, disposable syringes are recommended for those who mix insulins. If economy is important, you may reuse these safely several times. Insulin in use may be stored at comfortable room temperatures without loss of potency. Since we learned of the different rates of absorption of

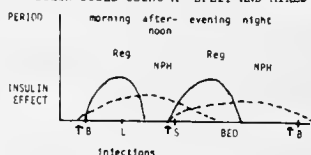
insulin injected into different sites, we have suggested rotation within regions before moving to a distant site. A patient with two daily injections might take the morning injection in the arm or abdomen (which more quickly release the insulin into the blood) and the afternoon injection in the leg or buttock. Exercise of an extremity also increases absorption, so we avoid injecting the leg just before running.

I believe it is more efficient for pa-

tients to adjust their own insulin doses when they can do so safely and comfortably. Changes in basal dose can be specified by an *algorithm* (a rule for making adjustments) such as the one in figure 3. Such algorithms are available for most common insulin regimens. This introduction of the concept of *feedback regulation* into the life of the person with diabetes represents an important advance over having the doctor make all the decisions. The decisions become more

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ADJUSTING INSULIN DOSES USING A "SPLIT-AND-MIXED" REGIMEN



ASSUMPTIONS

The morning short-acting insulin (REGULAR, SEMI LENTE, or ACTRAPID) has major action between breakfast and lunch, and its effect is reflected in the test results before lunch.

The morning intermediate-acting insulin (NPH, LENTE, or MONOTARD) has major action between lunch and supper, and its effect is reflected in the test results before supper.

The evening short-acting insulin has major action between supper and bedtime, and its effect is reflected in the test results at bedtime.

The evening intermediate-acting insulin has major action overnight, and its effect is reflected in the test results before breakfast the next day.

HYPERGLYCEMIA (HIGH BLOOD SUGAR) NOT EXPLAINED BY UNUSUAL DIET/EXERCISE/INSULIN

If urine sugars are positive or if blood glucose is over 140 mg/dl for ____ days in a row before lunch, beginning on day ____ increase your morning REGULAR (or SEMI LENTE, ACTRAPID) insulin by ____ units.

If urine sugars are positive or if blood glucose is over 140 mg/dl for ____ days in a row before supper, beginning on day ____ increase your morning NPH (or LENTE, MONOTARD) insulin by ____ units.

If urine sugars are positive or if blood glucose is over 140 mg/dl for ____ days in a row at bedtime, beginning on day ____ increase your evening REGULAR (or SEMI LENTE, ACTRAPID) insulin by ____ units.

If urine sugars are positive or if blood glucose is over 140 mg/dl for ____ days in a row before breakfast, beginning on day ____ increase your evening NPH (or LENTE, MONOTARD) insulin by ____ units.

HYPOGLYCEMIA (LOW BLOOD SUGAR) NOT EXPLAINED BY UNUSUAL DIET/EXERCISE/INSULIN

For hypoglycemic reactions or blood glucose measurement under 70 mg/dl occurring between breakfast and lunch, reduce your next morning's REGULAR (or SEMI LENTE, ACTRAPID) insulin by ____ units.

For hypoglycemic reactions or blood glucose measurement under 70 mg/dl occurring between lunch and supper, reduce your next morning's NPH (or LENTE, MONOTARD) insulin by ____ units.

For hypoglycemic reactions or blood glucose measurement under 70 mg/dl occurring between supper and bedtime, reduce your next evening's REGULAR (or SEMI LENTE, ACTRAPID) insulin by ____ units.

For hypoglycemic reactions or blood glucose measurement under 70 mg/dl which occur overnight, reduce your next evening's NPH (or LENTE, MONOTARD) insulin by ____ units.

Figure 3. An algorithm for adjusting insulin doses for patients using two injections of mixed insulin (a split-and-mixed regimen). The clinician tailors these guidelines for an individual patient by specifying the frequency and amount of dose adjustment to be made by the patient. Note that urine and/or blood glucose results may be employed. Errors in dose adjustment may be detected by the clinician at a periodic visit by review of a properly completed diabetes log.



monitoring diabetes makes sense

timely, and patients seem more willing to gather data for their own immediate use than for the doctor's later review. All components of therapy may need to be regulated for unusual exercise (less insulin and/or more food), acute illness (more palatable food, supplements of short acting insulin; we provide *Sick Day Guidelines* to explain this area in detail), changes in work shift, menstrual periods, or travel.

MONITORING diabetes makes sense to patients who use the information daily to make adjustments in therapy. Checking urine glucose remains the least expensive method, and can give excellent control in patients who spill glucose into the urine when the blood level of glucose is only moderately elevated and who

also recognize the symptoms of hypoglycemia accurately before the blood glucose falls so low that judgment is impaired. Those who continue to make some insulin in response to feeding may achieve normal blood glucoses at all times without monitoring blood glucose. The glucose oxidase strip methods are convenient and sensitive for those who rarely have positive urine sugar. The 2-drop Clinitest and Chemstrip μG methods are excellent for those who need to sample the range of 0-5% sugar. Self monitoring of blood glucose is recommended for those with an abnormal threshold, fear of — or inability to recognize — hypoglycemia, unusual instability, pregnancy or advancing complications (warranting intensive efforts to im-

prove control), or patient preference. Several visual strips and several meters give quite comparable results (accuracy $\pm 15\%$) provided technique is meticulous. It is important that each patient validate his accuracy with laboratory comparison after detailed instruction. Figures 4 and 5 show two popular logs for recording these results. They fit easily into a pocket or purse, and are arranged so that persistent elevations in glucose at a given time of day are readily recognized. It's a good idea to record any change in insulin dose in your log when you record the test result leading to the change. It seems easier to forget the adjustment if one waits until time for the next injection.

Periodic measurement of glycosylated hemoglobin by the physician

Month		Urine Sugar/Ketone (Acetoacetic Acid)								Medication		How Do I Feel Today?
Date	Day	A.M.		NOON		P.M.		BED		Dose/Time	Dose/Time	
		Sugar	Ketone	Sugar	Ketone	Sugar	Ketone	Sugar	Ketone			
1												
2												
3												
4												
5												
6												
7												

Figure 4. The Clinilog was developed by the Ames Company and is available via local pharmacies from Ames Clinilog II, Box 9706, St. Paul, MN 55197. Individual copies may be ordered for \$1 from Ames Clinilog II, P.O. Box 802, South Bend, IN 46624. Two weeks' results may be viewed at once. Although designed for urine sugar monitoring, it will accommodate blood glucose results or a mixture of urine and blood sugar recording in the generous blocks. It is important to record insulin dose at the top of each page, and again if there is a dose change. There is space for recording the time of hypoglycemia, unusual exercise, illness, stress, or other factors that may have altered control.

provides an additional check on self monitoring. This assay measures the fraction of hemoglobin in the red blood cells that has had sugar attached. This chemical reaction occurs in proportion to the blood glucose levels, so the assay estimates average blood glucose levels over a two month period. The test can provide useful confirmation of patient data. A marked discrepancy of glycohemoglobin result from glucose data is even more helpful because it provides new information. When urine or blood glucose results are known to be elevated, yet glycohemoglobin is normal or low, the explanation is often unrecognized hypoglycemia, most commonly during sleep. On the other hand, glucose estimates by the patient may be close to normal. In this case a markedly elevated glycohemoglobin may indicate invalid home testing from faulty technique, defective test materials, or recording fraudulent test results. We also recommend checking urine acetone at least before breakfast daily, regardless of the glucose result at the time. Ketones are produced when body cells are starved for sugar. You are familiar with ketone production during severe insulin deficiency (ketoadicidosis). Missing meals also in-

creases ketone production. When you are eating according to plan, a positive test for ketones when glucose is not elevated may provide a clue to earlier unrecognized hypoglycemia. Remember that ketones are produced in three different settings — insulin deficiency, lack of food, and insulin excess.

COMPLICATIONS are included in education so that they may be recognized and dealt with, or even avoided. Likewise, proper foot care, and knowing how and when to reach your doctor may help you avoid a prolonged hospitalization.

Contracts, Goals, and Problems

The treatment you receive for your diabetes must be the result of an understanding between you and your doctor about 1) how well you are doing as compared with your goals for control and 2) how hard you are willing to work to achieve control. If you feel well and most of your urine and/or blood glucose results are normal, and if these are confirmed by a normal glycohemoglobin measurement, you are to be congratulated; you have a successful diabetes regimen!

If you are accurately following your doctor's advice and have poor

control or other problems, your treatment program may need adjusting. There are many options. First, examine the basic program of diet and exercise, and make sure those are indeed correct. If oral agents fail despite these measures, your doctor will probably recommend insulin. If, despite correct measurement, mixing, injection, rotation, and dose adjustment, your insulin regimen works unevenly throughout the day (with high sugars at some times and low or normal sugars at other times), a more complex insulin regimen may be required. Today, two injections of mixed insulin is a fairly standard regimen, and we often recommend three or four injections to approach optimal control. Some patients may profit from using an insulin pump, which may offer more stable blood glucose control during the night and a bit more flexibility in the timing of feedings. Remember that such pumps, although programmable to deliver very complex regimens of insulin, are unaware of your blood glucose, and must be adjusted to change the regimen when your monitoring indicates the need. Other patients, with lipodystrophy (local wasting of fat at injection sites), insulin allergy, or insulin resistance may need the newer

Week beginning Monday: _____ (Date)

DAY OF WEEK	Type of Action	INSULIN INJECTIONS					MONITORING: BLOOD AND URINE										BG = Blood Glucose US = Urine Sugar UK = Urine Ketones NOTES:
		Insulin Code	Units Given	Mon	Tue	Wed	Thurs	BREAKFAST		LUNCH		DINNER		Bed Time	Over Night		
MON	Short Acting							BG									
	Longer Acting							US									
	SUPP							UK									
TUES	Short Acting							BG									
	Longer Acting							US									
	SUPP							UK									
WED	Short Acting							BG									
	Longer Acting							US									
	SUPP							UK									
THURS	Short Acting							BG									
	Longer Acting							US									
	SUPP							UK									
FRI	Short Acting							BG									
	Longer Acting							US									
	SUPP							UK									
SAT	Short Acting							BG									
	Longer Acting							US									
	SUPP							UK									
SUN	Short Acting							BG									
	Longer Acting							US									
	SUPP							UK									

*The Code letter appears on your insulin package

Figure 5. The Squibb-Nova Self-Monitoring Diary is designed for those who use multiple insulin doses. Supplements are recorded separately to reduce the risk of accidental inclusion in the basal dose for the following day. As many as eight monitoring times during the day may be used without impairing the ability to compare one day with another. This log is available through physicians, some pharmacies, and the Squibb-Nova company.

highly purified animal or human insulins. As prices of these insulins fall, we may recommend them routinely for patients beginning insulin therapy, or even for all patients requiring insulin.

Summary

I have reviewed for you what I call Stepped Care for diabetes mellitus.

This simply means beginning with basics and doing, step by step, what is necessary to achieve the goal level of control agreed on by doctor and patient. Some of you will require many more of these steps than others. Managing one's diabetes is a challenge; there is a lot to deal with. Now, fortunately, we have more ways than ever of attacking the problems di-

abetes presents. Join in my optimism that diabetes management will continue to become more effective and may someday even be easier!

Reference

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Psoriasis

Claude S. Burton, M.D., Peter W. Heald, M.D., and J. Lamar Callaway, M.D.

Thanks to Madison Avenue, we are all familiar with the "heartbreak of psoriasis." For 1-2% of Americans this noncontagious skin disease is more than familiar and varies in presentation from a minor cosmetic nuisance to a disabling and rarely fatal illness. There is neither a cure nor a universally successful treatment. By careful selection from a great number of useful therapies (and some trial and error), psoriasis can be satisfactorily controlled in virtually every case. Many of the medications we discuss are available without prescription and milder cases may respond to self-treatment. When self-treatment fails, or when the disease worsens, professional help is essential.

Whether you pursue self-treatment or a professionally guided approach, our limited knowledge of this disease will help you manage the disease. Psoriasis is a disease influenced by genetic and environmental factors. Many but not all patients have a family history of the disease and many but not all patients can relate the onset of their psoriasis to a strep throat, viral infection, or trauma to the skin such as multiple wasp stings, sunburn, etc. Alcohol, certain drugs (Lithium, Inderal, other betablockers), and emotional stress are common flare factors and should be avoided by all people with psoriasis.

In skin affected by psoriasis the epidermis or outer layer proliferates very fast. Whereas normal skin completes a growth phase roughly every 20 days, psoriatic skin completes this process every 24-48 hours. All of the therapies of psoriasis are aimed at

slowing this growth. Psoriatic skin is red due to the increase in blood flow in the region and scaly due to the rapidly accumulating epidermis. These red spots with silver scale on their surface are unsightly and often itch intensely. If large surfaces are affected, fluid and nutrient loss may be significant and the increased blood flow through the skin may strain the heart. Any or all of the skin may be involved. Elbows, knees, and other sites of friction are common sites of involvement. The scalp is another common spot and many patients with psoriasis are seen in the office for intractable "dandruff." Arthritis is often seen in psoriasis patients, indicating the possible systemic nature of this disease.

The name "psoriasis" comes from the Greek word for "itch." Psoriasis antedates the Greeks, however, and apparently has been with us at least since man began to write. Early authors grouped this condition with leprosy, adding to the misery of countless individuals with psoriasis. The shame and embarrassment associated with psoriasis continues to be a major problem for anyone with the disease. Ironically, this embarrassment prevents many psoriasis sufferers from enjoying the dramatic effect of sunlight on this disease.

Sunlight is the cheapest of the available therapies. If the areas of involvement are exposed to the sun, a complete remission of the disease may occur after several weeks or months of treatment. Since psoriasis often involves parts of the body considered private, and since many patients are too embarrassed by their appearance to sunbathe, artificial sunlight in the form of an ultraviolet light cabinet or a portable sunlamp is

a useful alternative to natural sunlight. These artificial sources have the advantage of year-round, weather-independent availability. Ultraviolet light is not without hazard: premature aging of the skin and the risk of skin cancer are causes for concern. A sunburn, which will flare psoriasis in many cases, is a threat with both natural and artificial ultraviolet light. Carefully graduated exposures are recommended. A number of spas around the world are dedicated to this climatic therapy. One such spot located on the Dead Sea has reported a response rate of 96%.

Oral doses of plant compounds known as psoralens markedly potentiate the effects of ultraviolet light. These agents are taken by mouth two hours prior to light exposure in a special cabinet producing light in the ultraviolet A range of the light spectrum. Ultraviolet A light transforms the circulating psoralen into a molecule that is toxic to the rapidly dividing psoriatic epidermis. Though effective in over 90% of patients, the therapy is not for everybody. In addition to the hazards of ultraviolet light, there is a risk of early cataract formation. Patients are required to wear filtering glasses on the day of treatment to prevent activation of the ingested psoralen as it circulates through the eye. PUVA (Psoralen + Ultraviolet A) is expensive and often inconvenient due to distant treatment facilities and the time required for therapy and necessary precautions.

Topical steroids relieve the itching but they are expensive, messy, and associated with undesirable thinning of the skin, rapid and exaggerated relapse, and in some cases systemic absorption. Still, topical steroids are useful in breaking the "itch/scratch"

From the Department of Medicine, Duke University Medical Center, Durham 27710.

cycle that may worsen psoriasis and in suppressing symptoms during the early stages of the other therapies. Hydrocortisone cream is available over-the-counter, but the more potent topical steroids require prescription.

Crude coal tar in various topical formulations (many are available over-the-counter) slows the growth of psoriatic epidermis and relieves the itch for many patients. These remedies smell bad and are extremely messy for home use. Crude coal tar is a mix of some 10,000 compounds. One of these, anthralin, when extracted from tar, is much more effective than crude coal tar but requires a great deal of skill and time to use. Anthralin (prescription only) is applied to involved skin for varying amounts of time depending on patient tolerance. Anthralin slows the growth of the psoriatic epidermis and in time is capable of inducing a remission of the disease. Anthralin is extremely irritating to normal skin especially in body folds. It turns a dark brown on exposure to air and the staining of fabrics and in some instances bathroom appliances is

permanent.

All of these topical and photo therapies are time-consuming and limited in usefulness by the associated mess. Though effective and reasonably safe, they do add to the nuisance associated with the disease. An alternative to these topical and photo treatments is oral agents. Of the many drugs under study methotrexate has emerged as the single most effective oral therapy for the treatment of psoriasis. Methotrexate, an antagonist of the vitamin folic acid, slows the growth of the psoriatic epidermis and is effective where other treatments have failed. Methotrexate is also very effective at controlling the arthritis associated with psoriasis. The use of methotrexate in low doses by mouth one day a week was pioneered at Duke by Dr. J. L. Callaway in the early 1950s. An informal poll of dermatologists suggests that this approach would be their choice for personal treatment if they had recalcitrant psoriasis. Although methotrexate is a marvelously simple therapy, skill in appropriate use of the drug is critical

to its safe use. Laboratory studies (which add to the expense of this treatment) must be monitored until a steady response to the drug is established. Liver toxicity may occur in some patients particularly in association with a prior history of liver damage or in persons who drink moderate to heavy amounts of alcohol. The only way presently to monitor for this complication is by examination of needle biopsy specimens of the liver. Since liver biopsy is expensive and potentially dangerous, newer methods of monitoring for liver toxicity are being explored. Our group is studying the use of a new technique, nuclear magnetic resonance scanning (NMR for short), as an alternative to liver biopsy. NMR scanning does not require biopsy or needles of any sort, does not expose the patient to radiation, and may be accomplished as an outpatient at a fraction of the cost of liver biopsy.

With the advent of new techniques it is likely that psoriasis therapy will soon enter a new era of simple and effective therapies. Though the cause and cure elude us, we are in hot pursuit of both.



IT'S GETTING TOUGHER FOR NANCY RAY TO BE A MOTHER.

Nancy Ray has multiple sclerosis.

Every day it becomes harder for her to see. Harder for her to walk. Harder to do the things she wants to do for her family.

Four years ago, Nancy Ray was young and healthy. She was a mother with a four-year-old son, a teacher, a writer for educational TV.

Then, like about 200 young adults every week, she learned she had MS.

Multiple sclerosis destroys the myelin covering that surrounds nerve fibers in the brain and spinal cord. Messages to and from the brain get lost as they travel through the damaged area. So your eyes, arms, legs don't do what you want them to do.

MS can be mild. Or it can be severe. Once you've got it, you've got it for life. Most days, Nancy Ray can get around with a walker. With a lot of time and effort, she can even prepare meals for her family. Some people with MS aren't that fortunate.

The National Multiple Sclerosis Society is helping people with MS live with MS. And funding research for a cure, all over the world. We can do it, but only with your help.

Please give generously. It's tough enough to be a mother without MS.

**NATIONAL
MULTIPLE SCLEROSIS
SOCIETY**

205 East 42nd Street
New York, New York 10017

JUST WHEN YOU'RE STARTING TO LIVE, MS CAN STRIKE

Black Dermographism

Lester J. Fahrner, M.D.

- *An interesting and insignificant finding of black coloring on the skin after stroking it with good gold jewelry.*

CONDITIONS of no pathologic significance are often brought to our attention by our patients. These medical curiosities are sometimes a matter of concern to the patient. Probably just as often, the person considers the problem almost too inconsequential to mention to a doctor. We recently had the opportunity to see a patient with an unusual but insignificant finding.

At the end of a recent visit, a 36-year-old white woman mentioned that her children sometimes amused themselves by drawing on her skin with 14 and 18 carat gold jewelry. Her face or hands would be colored black wherever the gold was stroked. (See cover photos.) The pigment would slowly fade away over a few hours, or could be easily rubbed or washed off. "Cheap gold" or costume jewelry had no effect at all. She asked if we had heard of this before, and if we knew what caused it.

In the days after our interest was aroused by this patient, we saw a number of people with black coloration of the skin around their rings and on the fingers adjacent to those on which rings were worn. None of our other patients could easily draw on the face the way our original patient can.

We are all aware of the more common "problems" that jewelry can cause. Copper oxides and salts leached from inexpensive jewelry can stain the skin green. Moisture and soap trapped beneath rings and bracelets frequently leads to an irritant dermatitis. Allergic contact dermatitis due to nickel is commonly seen in areas under earrings, wrist-watches, bracelets, etc.

Gold is quite inert chemically, both regarding oxidation and ionization. It is also soft, malleable, and easily polished to a fine sheen. These properties have contributed to its place as a most desirable precious metal. It was hard to imagine how gold caused our patient's dark lines. A glance at the dermatologic literature led to an appreciation of the phenomenon of black dermographism.

From the Department of Medicine, Duke University Medical Center, Durham 27710.

Black dermographism was first reported in 1925 in the Russian literature. The nature of the condition was debated over the next five years in the German and Russian dermatologic journals. Various physical and chemical theories were put forth, some of which postulated that the patients were necessarily hypothyroid, neurotic, or hysterical. The initial patients were women who wore facial powders. Workers in some dusty occupations were later found to also exhibit black dermographism.

Urbach and Pillsbury¹ tested a number of finely powdered salts and commercially available face powders for their ability to induce black dermographism. When applied to the skin, coarse cloth, and filter paper, all the cosmetics and many of the metal salts made a satisfactory substrate for producing black lines when drawn on with metal objects made of silver, gold, copper, and many others. They proved with photospectrometric analysis that the black color is indeed the metal which has rubbed off onto the skin, paper, etc. All transition metals, when finely divided, appear black.

Optimal conditions are those that will lead to maximal friction: low lipid content, relative freedom from eccrine sweat, and intentional or incidental coating with a finely divided metal salt or oxide. Soft metals such as lead, silver, and fine gold "draw" more readily. Knowing this I thoroughly washed and dried my hands, dusted the dorsal surface of my hand with my wife's face powder, and rubbed black lines on my skin with an 18 carat gold ring. The color washed off easily.

If patients mention black coloration from their gold or silver jewelry, they may suspect "too much acid in the system," or that their loved ones are bestowing inexpensive gifts. You can explain that they are seeing a common, normal effect of metal rubbing against the skin.

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Insulin Can Make Diabetes Worse: The Smoldering Somogyi Effect

Linda M. Frazier, M.D. and Francis A. Neelon, M.D.

• *Nocturnal hypoglycemia can cause rebound hyperglycemia.*

DOCTORS have traditionally relied on measurement of urine glucose and fasting blood sugar to adjust insulin therapy; if the glucose is high, more insulin is prescribed. Paradoxically, this approach may sometimes result in even higher blood sugars. The following case illustrates how diabetic control may remain poor until the insulin dose is lowered.

A sixty-one-year-old man had a fifteen-year history of diabetes mellitus treated with insulin, 49 units (U) daily in two doses composed of a mixture of NPH and regular insulin. Fasting blood sugar ranged from 130 to 211 mg/dl (normal 75-110). His course was complicated by recurrent depression and during the nine months before admission he noted decreased appetite and difficulty falling asleep; he lost four pounds. He had occasional episodes of weakness, sweating, and palpitations, and was twice found wandering about his house with a glassy expression. One day he became confused while driving and crashed into a stopped truck. There was no loss of consciousness or seizure activity; his sensorium cleared spontaneously. He did not use alcohol.

On admission he was alert and oriented; physical exam was unremarkable. A mid-morning blood sugar was 297 mg/dl; creatinine was 1.0 mg/dl (normal 0.7-1.4) and thyroxine was 9.6 (normal 5.5-11.5). We suspected hypoglycemia precipitated by decreased food intake and used a Glucometer to monitor blood sugar in fingerstick blood samples at bedtime and at 3 a.m. We decreased insulin to 47 U daily in two doses of mixed NPH and regular insulin. The 3 a.m. blood sugar ranged from 44 to 80 mg/dl while afternoon and evening glucoses rose as high as 436 mg/dl. Fasting blood sugars (6:30 a.m.) were normal to slightly elevated, but episodes of hypoglycemia, especially at 2:00 or 3:00 a.m., were frequent, leading us to progressively decrease the total prescribed dose of insulin.

As the total daily insulin dose gradually decreased, peak serum glucose fell toward an acceptable range (figure 1). When hypoglycemia occurred at night, the blood sugar rose sharply the next day despite insulin administration (figure 2). When nighttime hypoglycemia was avoided, the blood sugar the next day was lower even though less insulin had been given (figure 3). When we reached seventy percent of

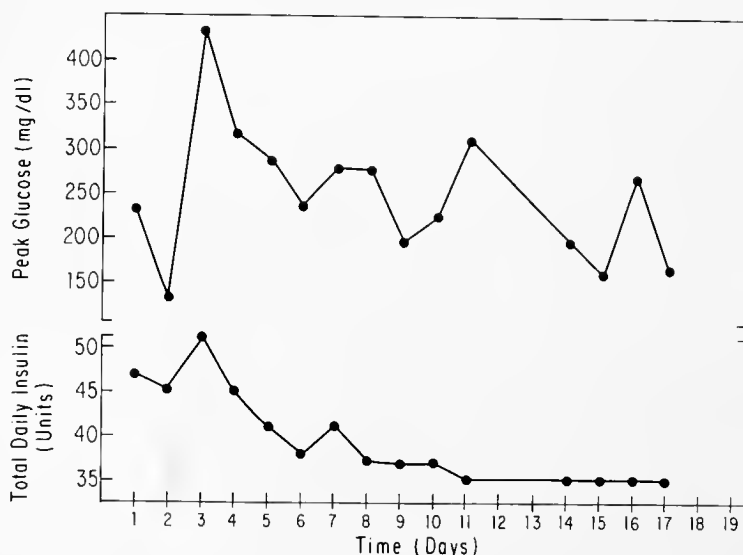


Figure 1. Relationship of peak glucose each day and total daily insulin dose.

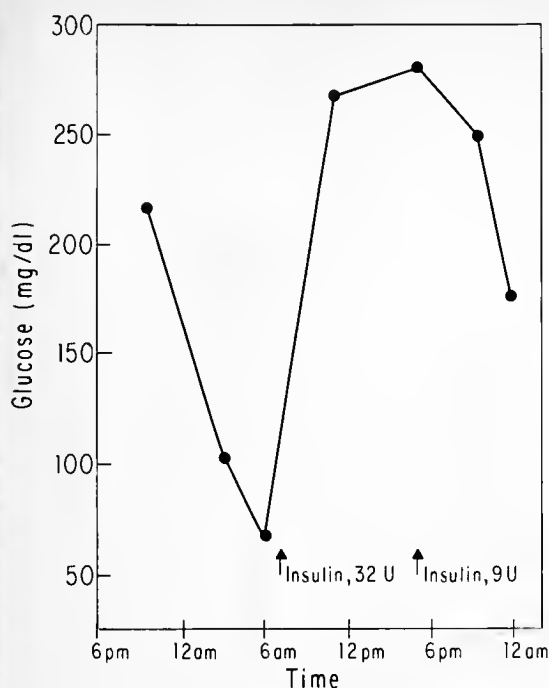


Figure 2. Hypoglycemia causes glucose elevation despite substantial doses of insulin (hospital day 5).

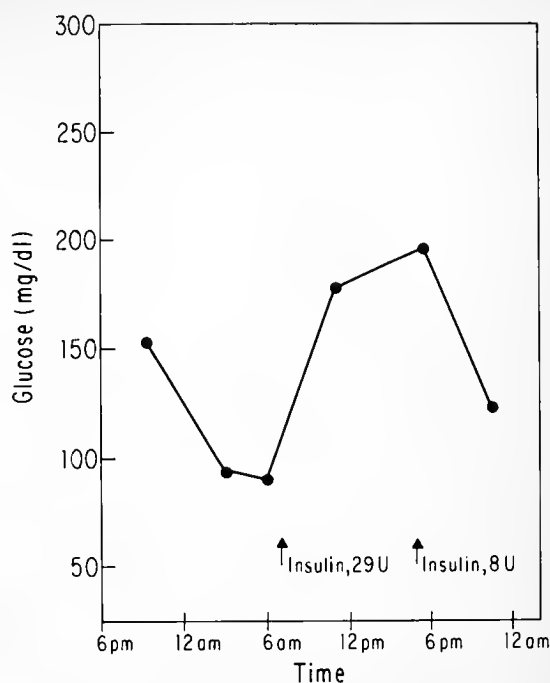


Figure 3. Improved glucose control in the absence of hypoglycemia (hospital day 9). Afternoon blood sugar is lower than on day 5 (figure 2) despite a lower insulin dose.

his previous insulin dose, hypoglycemia resolved and further adjustments were begun as an outpatient. The episodes of confusion stopped.

If we had not measured blood sugars at 3 a.m., we would have been tempted to increase his morning insulin in an attempt to control afternoon hyperglycemia. This would only have exacerbated nocturnal hypoglycemia and worsened diabetic control. Hypoglycemia causes several hormones to be released which have an "anti-insulin" effect including catecholamines, glucagon, growth hormone and glucocorticoids.¹ Catecholamines, glucagon and cortisol increase hepatic gluconeogenesis; catecholamines impede insulin release and peripheral glucose utilization. Hypoglycemia results in rebound hyperglycemia which will recur until hypoglycemia is eliminated. Keep in mind, however, that on the day *after* hypoglycemia, insulin needs are actually, but transiently, increased so no reduction in insulin dose should be made until the hyperglycemic rebound has passed.

The phenomenon of diabetes made worse by too much insulin was first observed by Michael Somogyi, a biochemist, in 1935.² At that time, mild hypoglycemia was felt to be harmless or perhaps even beneficial for diabetic patients. Insulin therapy was adjusted according to quantitative urine glucoses; when the urine contained large amounts of sugar, the insulin dose was rapidly increased. Dr. Somogyi studied several patients who were classified as "unmanageable" diabetics despite receiving insulin in doses of 95 to 150 U per day. He found that glycosuria followed a distinct pattern:

... high glycosuric tides tended to follow days when the sugar in one or two urine fractions was close to zero, even though the spill for the entire day may not have been conspicuously low. . . . A fact that impressed us and was very significant was that glycosuria flared up with especial violence in the wake of pronounced hypoglycemic reactions.²

When Somogyi substantially reduced total insulin dosage, twenty-four hour urine glucose fell and fluctuated less from day to day.

The Somogyi effect should be suspected in compliant but poorly controlled diabetics even when they do not report frank hypoglycemic symptoms. Gale and Tattersall found nocturnal hypoglycemia in 22 of 39 poorly controlled diabetic patients;³ six of these were asymptomatic. Patients with symptomatic hypoglycemia reported lassitude or depression, night sweats, undue difficulty in waking, early morning headaches, nocturnal seizures or vivid or disturbing dreams. Hypoglycemia at night does not mean that the routine morning "fasting blood sugar" will be low. In fact, Gale and Tattersall found only one patient to be hypoglycemic on routine blood sugar before breakfast. In the absence of symptoms, morning hypothermia or ketonuria without heavy glycosuria may be clues to unrecognized nocturnal hypoglycemia. In all cases, physicians need a high index of suspicion, especially in patients receiving more than 1.2 U insulin/kg/24 hours, although elderly patients become hypoglycemic at lower doses than this.

To diagnose the Somogyi effect before home glucose

monitoring became available, admission to the hospital was usually necessary for measurement of serum glucose around the clock. Several companies now market kits that allow patients to estimate blood glucose by the colorimetric change caused by a drop of blood placed on a strip of reagent-impregnated paper. Machines such as the Glucometer use this principle to provide a precise digital read-out of blood sugar. These instruments are easy to use, are becoming less expensive, and are sometimes partially reimbursable by insurance. They give patients with di-

abetes a measure of control over their condition that Dr. Somogyi would have envied.

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LEARNING WITHOUT WORDS

New Wine in Old Bottles

Francis A. Neelon, M.D.

- *A change in the formulation of Synthroid tablets may lead to inadvertent overdosage*

OCCASIONALLY drug manufacturers, in an attempt to improve their products, do an unwitting disservice to the patients who take those drugs. A recent change in the formulation of Synthroid (sodium levothyroxine) is an example of this as illustrated by the following case:

A thirty-five-year-old woman had had a thyroidectomy several years previously. She had a history of radiation treatment in childhood and the discovery of a goiter properly resulted in a recommendation for surgical removal of the thyroid. A microscopic papillary thyroid carcinoma was found although the clinically evident goiter had been due to Hashimoto's thyroiditis. There was no evidence of metastasis and the only treatment indicated was suppression of thyroid function with oral thyroxine.

For the past four years she has been on a constant dose of Synthroid (0.175 mg/day), a dose that has successfully suppressed thyroid stimulating hormone (TSH). After correction for thyroxine binding globulin concentration,

serum thyroxine (T_4) had been slightly higher than the normal range, but serum triiodothyronine (T_3) had been within the normal range and the patient asymptomatic until last year when she experienced unexplained weight loss. Measurement of serum thyroid hormones showed a dramatic increase in T_4 and a T_3 value clearly above normal (figure 1). She had made no change in the prescribed Synthroid dosage and had faithfully taken the tablets as directed.

The explanation for this unanticipated result is contained in a letter to me from Dr. David L. Horwitz, Medical Director of Flint Laboratories in which Dr. Horwitz explains that Flint has indeed changed the formulation of Synthroid tablets and now uses a radioimmune assay to standardize the tablet size. The new procedure provides a more accurate dose and, in itself, is laudable. What is unfortunate is that the new tablets contain more thyroxine than the old (Dr. Horwitz thinks the change should not be clinically significant). Dr. Horwitz to the contrary notwithstanding, some patients (especially those maintained purposefully at the limit of tolerance) may become thyrotoxic

From the Department of Medicine, Duke University Medical Center, Durham 27710.

as I believe my patient has. Apparently other physicians have experienced problems similar to mine, because a recent issue of the *Medical Letter* (Volume 26, Page 41, 1984) cautions us to be alert to potential thyroxine overdosage in patients on Synthroid. Patients taking Synthroid

should have their serum thyroid hormone concentrations checked and the prescribed dose changed if indicated. We also may have to recalculate the old rule of thumb for thyroxine replacement dosage (0.001 mg/lb body weight).

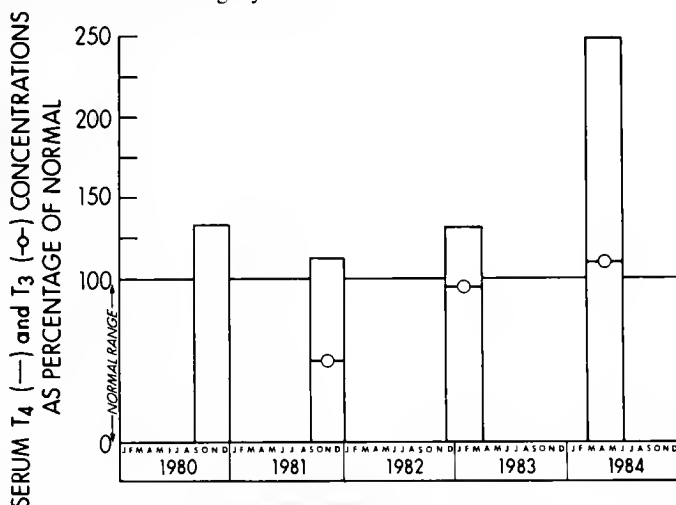


Figure 1. Serum thyroxine (T_4) and triiodothyronine (T_3) concentrations, corrected for protein binding and expressed as percent of normal range, in a young woman maintained on a constant prescribed dose of Synthroid. In 1982 the manufacturer reformulated the tablets and those now reaching the marketplace contain more thyroxine than previously.

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From Grandma to Galen: Boric Acid Poisoning

Ronald B. Mack, M.D.

I believe that the spirit of Galen still lives!! Where, you ask? Why in the DNA of the world's grandmothers and great-grandmothers, of course. Galen of Pergamum, who lived from 130 A.D. to 201 A.D., was probably the second most famous of the ancient Greek physicians; Hippocrates is clearly the Oscar winner here.

Galen's major theory, which was primarily an elaboration of the works of Hippocrates and Aristotle, proposed that the human body was composed of four vital elements: *fire, air, earth and water*. These components made up the four major humors of the body: *blood, phlegm, black bile and yellow bile* (if you are reading this while you are eating, I apologize). Each of the humors had very definite qualities: *blood* was considered moist and warm, *phlegm* was moist and cool, *yellow bile* was warm and dry, and *black bile* was cold and dry.

The deficit or excess of a humor or humors was thought to determine health and temperament, e.g., blood = sanguine (cheerful, optimistic); phlegm = not easily excited, "cool"; yellow bile = choleric, irascible; and black bile = melancholy. Thus, the underlying cause of disease was viewed as a morbid state of the humors which were considered to be impure or in excess or in deficit or displaced. The treatment for a given disease depended on the state of the humors. If a humor or humors were excessive the patient was treated by depletion via bleeding, purging, sweating, etc. If the humor or humors were deficient the patient could be helped by attempting to restore the deficit by diet or medications. Galen classified drugs, accordingly, into groups that possessed one or more of the qualities of warmth, dryness, coldness, wetness. These drugs could be applied whenever a deficiency or excess of one or more humors mandated a counter action.

The teachings of Galen remained unchallenged until the time of Paracelsus in the 16th Century. In Colonial times in this country and well into the early 20th Century, Galenism was still quite popular. I believe the teachings of Galen still persist today in many segments of our population. The only way you are going to determine which of your patients are using these methods is to ask questions of them unless they volunteer the information without prodding (rare in my experience). It is most often a grandmother or great-grandmother who advises the younger members of the family to try a remedy that has "always worked before." It is a fair statement, I believe, that most people in this

country do something to try to alleviate their symptoms before seeking professional medical aid. Some of the treatments they utilize would make Galen very proud indeed.

One of my most unfavorable medications is *boric acid*. Yes, it is still quite available and in the recent past we have had several calls concerning boric acid ingestion. Often the use of this terrible stuff has been recommended by grandma. (I apologize for seeming to be harsh on grandmothers. I love them!! I go to bed with one every night.)

Poisonings due to borates are not as common as they used to be, thank goodness, but occasionally cause problems both for the victims and their medical caretakers. These chemicals exist in both alkaline and acid forms. Sodium borate (AKA borax) is used as an antiseptic and a cleansing agent. The perborate form is used as a mouth wash. Boric acid was first used as an antiseptic by Joseph Lister in 1875. It is typically prepared by mixing sulfuric acid with sodium borate. This chemical is still used as an antiseptic and as an agent to make talcum powder flow more readily. Those of us old enough to remember can still recall using a boric acid solution to "wash our eyes" when we had "pink eye." (We used a device called an eye cup. I forgive you mother if you are reading this!) Boric acid solutions were also used as wet dressing for patients with thermal burns, diaper rash, skin ulcers and surgical wounds. This chemical was available in nurseries where it was responsible for many deaths because it was inadvertently used in infant formula preparation (because it resembles sugar, etc.). Nursing mothers were advised to wash their nipples with a boric acid solution before breast feeding. It is alleged that in the past it was used in the treatment of epilepsy.

Boric acid is not a good antiseptic as it is only mildly bacteriostatic. It probably is not good for anything. It is a wonder that it still is available to the unwary consumer. In my opinion it should be removed forever. Many of my patients use urine as a medicine, e.g., for tinea capitis, ear pain, oral candidiasis and contact dermatitis; it is probably safer than boric acid and just as much an anachronism. You can purchase this acid in powder or liquid form. Borates are easily absorbed from abraded or diseased skin, mucous membranes, and the GI tract. Many cases of poisoning in the past resulted from percutaneous absorption of the boric acid in the treatment of diaper rash.

The pathophysiology of boric acid poisoning involves the GI tract, CNS, skin, liver and kidneys. The kidneys are probably the most seriously affected of all the organs involved. Boric acid is said to be toxic to all cells but the

From the Department of Pediatrics, Bowman Gray School of Medicine, Winston-Salem 27103.

mechanism of toxicity is unknown. The fatal dose is thought to be about 5-6 grams in an infant and 20 grams in an adult; it is fatal at about 0.1-0.5 gram per kilogram according to some authorities. In acute boric acid poisoning the clinical features can be quite frightening but of course non-specific. Early on, the vomiting and diarrhea of blood get your attention as well as the often severe colicky abdominal pain. Initially the effect on the CNS results in malaise, lethargy, restlessness, headache, tremors, and even seizures. In more severe cases coma ensues. Fever and tachypnea are quite common with increasing respiratory difficulties leading to arrest. The injury to the kidney is usually a renal tubular necrosis manifested by oliguria or anuria, and albuminuria. Jaundice is not common but is a possibility.

In my opinion, the most interesting toxic event in boric acid poisoning is the dermatological sequelae. The skin becomes quite erythematous with vesicles or papules appearing on the hands and ultimately becoming generalized. This results in what is referred to as the "boiled lobster" appearance (I don't care, I'm not going to give up eating lobster). The skin lesions advance to bullae formation followed by desquamation and sloughing. This is indeed the classic picture of boric acid poisoning and its presence should alert you to the possibility of this diagnosis. The skin lesions are not pathognomonic, of course, and do resemble scarlet fever or toxic epidermal necrolysis.

The diagnosis is usually a clinical effort; laboratory confirmation is not easy to obtain. Blood samples from victims of suspected boric acid poisoning can be analyzed without charge by the U.S. Borax and Chemical Corporation;¹ 10 ml of clotted blood (without an anticoagulant) should be sent via air-mail to Russell S. Fischer, M.D., Chief Medical Examiner, State of Maryland, 111 Penn Street, Baltimore, Maryland 21201.² Send the sample in a polyethylene bottle with a case summary. The company advises you to take an initial blood sample as soon as possible after the ingestion, another 24 hours post ingestion, and repeated samples as needed to determine a trend. Dr. Fischer is the Medical Consultant for the U.S. Borax and Chemical Corporation.

A rapid qualitative test requires one drop of the patient's urine acidified with HCl and applied to tumeric paper. This paper turns brownish-red if boric acid is present.

The urine often has red blood cells, protein, and epithelial casts in boric acid poisoning. Urine function and liver function tests should be monitored.

The treatment is less than thrilling; of course there is no antidote. Anything you do for the patient is usually only supportive. In ingestions that have occurred fairly recently, gastric emptying followed by activated charcoal is probably of some value. Dr. Fischer suggests the administration of glucose either orally as in "sweetened drinks" or by IV if the patient's condition warrants. He also suggests frequent monitoring of the patient's urine for rbc's.³ Seizures can be controlled with diazepam. Needless to say, the maintenance of fluid and electrolyte balance is clinical here. Fortunately for all of us, boric acid lends itself to removal by dialysis, either peritoneal or extracorporeal. It is difficult to know when dialysis is indicated in these cases; blood levels are probably of no help here (even if you could get the results quickly enough); clinical judgment is the name of the game.

Maybe Galen wasn't such a bad guy after all. Plenty of people still practice his principles, e.g., many of our patients routinely take laxatives or give them to their children (whether they need them or not) to remove the "poisons or waste." In many Eastern European countries "cupping" is still in vogue. How many of your patients use chest rubs such as Vicks or use a mustard plaster on the chest? The most ubiquitous home remedy in our clinic in my experience involves the use of onions as a poultice, in the shoes or socks, in a hat, as a necklace, under the bed, as a drink, etc. Why I don't know, but Hippocrates spoke well of onions. Anyone who uses them medically should probably not be allowed to enter the 21st Century. Come to think of it, boric acid should not have been allowed to enter the 20th Century.

Let us not be so smug. Galen lives on in us as well, lest we forget "bleeding" via phlebotomy, dialysis, hemoperfusion, and plasmapheresis and "purging" via ipecac and saline cathartics. (I love it!!)

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3. Personal communication, Dr. Russell Fischer.

Before prescribing, see complete prescribing information in SK&F CO. literature or PDR. The following is a brief summary.

WARNING

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K⁺ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K⁺ intake. Associated widened QRS complex or arrhythmia requires prompt additional therapy. Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak local acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Anti-hypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

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Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, parosmia, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

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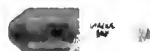
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Changing Perceptions of the End-Stage Renal Disease Program

William B. Blythe, M.D.

Dr. Robert Gutman's article "Renal Dialysis for Kidney Failure in North Carolina: History, Practice, and Lessons"¹ in this issue of the *Journal* should be read and carefully contemplated not only by nephrologists but by all physicians. Contained therein is an account of the development of a life-prolonging biomedical technique, dialysis and, more importantly, an account of how our society has responded to its development. The technique and the reaction to it have become interwoven into a federally administered endeavor known as the End-Stage Renal Disease Program.

Dr. Gutman's paper and the End-Stage Renal Disease Program as it now exists raise important questions, some of which may be answerable now and some of which have more elusive answers, but all of which are sober and sobering. Furthermore, not only the answers but even the selection of the critical questions are to a large extent determined by one's profoundly held view of the nature of government, economics, and — ultimately — the nature of man.

Thus, as Dr. Gutman suggests, the lessons to be learned from the blemishes and warts as well as from the comeliness of the End-Stage Renal Disease Program may be, as is the perception of beauty, determined mostly by the outlook of the beholder.

I have been involved in planning for dialysis in North Carolina from the start some two decades ago. It is telling that those of us who have been involved that long have seen the cause for anguish change emphatically through the years. Early on it was the sad fact that dialysis was available to only a fraction of those who needed it. Lately it appears to derive from a perception in many quarters that 1) dialysis is not only available to all who need it, but is being employed in many cases where it may be of little help and 2) the cost of the End-Stage Renal Disease Program is either more than we can afford or more than it should be.

Why have we come to this position? First, what about the difference between the characteristics of patients who were selected for dialysis in the mid-sixties and those who are being selected for dialysis in the mid-eighties? As Dr. Gutman points out, patients who were selected for dialysis in the days of limited funding were younger and relatively free of complicating illness. This does not mean, it should be remembered, that older patients with complicating illness such as diabetes mellitus and hypertensive cardiovascular disease were not dying from end-stage renal

disease. It does mean, in my judgment, that reality, in regards to the distribution of renal disease and the demographic characteristics of patients suffering therefrom, was not properly perceived by many responsible people.

In 1972, with passage of federal legislation that virtually eliminated money as a factor in selection of patients, reality began to be appreciated. It became clear in North Carolina that most of our patients had end-stage renal disease as a consequence of hypertension or diabetes mellitus and that most were older than we had thought. The medical decisions as to who was acceptable for dialysis became more difficult. Medical criteria therefore understandably became more liberal. I am certain that pitifully few — if any — patients have been accepted by nephrologists in North Carolina solely for financial gain; rather their dialysis rolls have been increased by the sicker and older because they had been there all along but now were clearly evident.

Furthermore, as one would reasonably predict, as the sicker, older and less sophisticated became an increasing percentage of the dialysis population, the percentage returning to gainful employment or acceptable rehabilitation decreased. It must be made clear, in addition, that this has not been solely a function of the degree of medical rehabilitation. Government regulations concerning disability, employer attitudes, and time away from work because of dialysis as well as other factors have played a major role. Thus, until we know considerably more about all these determinants, it is unreasonable to damn the End-Stage Renal Disease Program on this score. Drs. Gutman, Stead and Robinson² have made a major contribution in this regard and have set the stage for further dissection of the problems. It is imperative that we find out exactly what the situation is.

Now, what about the cost of the program? It is expensive. The cost of the End-Stage Renal Disease Program in 1984 will approximate 3 billion dollars. The increase in cost over the past decade has not, in general, resulted from an exorbitant rise in expense per patient, as Dr. Gutman reminds us, but rather from the tremendous increase in the number of patients who are in chronic dialysis programs.

Nevertheless, to my knowledge, no supplier of dialysis equipment, no corporation that has built and run dialysis units, no hospital and no nephrologist who operates a dialysis unit and/or cares for patients in dialysis programs has been close to financial exigency because of involvement in the program. Thus, I suspect, with a high degree of certainty, that there is still financial fat in many aspects of the program that can be safely cut away from the critical lean. This has to be done! But even if this were accom-

From the Department of Medicine, The University of North Carolina, Chapel Hill 27514.

plished in ideal fashion, the program would still be quite expensive.

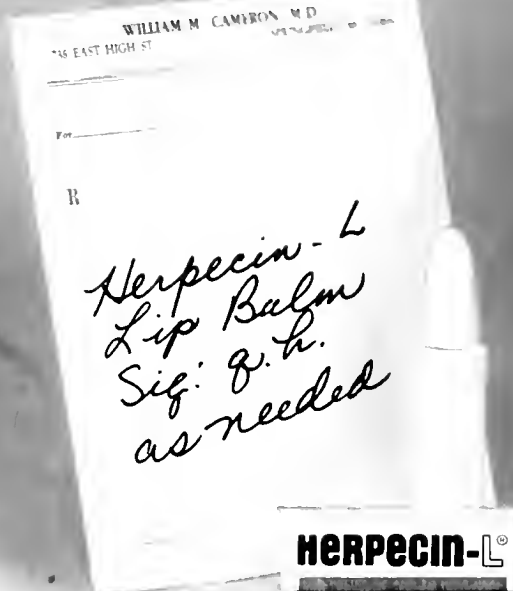
And then, in my judgment, the question becomes: How expensive is dialysis in relation to other things that government — and hence, society — undertakes? For example: public schools, aircraft carriers, super highways, military defense in outer space, education for physicians, bureaucracy, national parks, military aid to dictatorships, and on and on. I believe that we can afford it.

Finally, we must not forget that chronic dialysis is only an interim solution. Renal transplantation, all would agree, is the penultimate answer, and prevention of renal disease the ultimate one.

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Human Experimentation: The Ethical Dilemma

John B. Graham, M.D.

THE most succinct definition of ethics I ever heard was at a meeting of a pathology society, when in his presidential address, the president defined ethics and morals for the assembled pathologists this way: "When I hear you discussing ethics and morals, the definitions seem very simple. Ethics has to do with money, and morals has to do with sex."

A more enlightening if less humorous experience came during temporary service on the ethics committee of the American Heart Association. One of my colleagues in Chapel Hill had served on this committee for a number of years and wished to be relieved. He suggested that I be considered as his replacement, and arranged for me to be invited to Dallas for vetting, where I was asked to discuss the relation of genetic factors to heart disease. I listened to the discussion, mostly between doctors, with mystification for two days, then asked what was to me a simple question, but it shook them. I do not know whether they were shaken because of my ignorance or my naivete, but no one answered the question and I was not invited to return.* The question I asked was: "What should be the basis of medical ethics in a pluralistic society?" The lack of response surprised me, because this question has puzzled me for so many years. I suppose I should not have been surprised subsequently when I observed that theorizing about medical ethics had been taken away from physicians by lawyers and philosophers. My experience suggests that even a carefully selected group of doctors is unable to deal very effectively with such complex matters. Perhaps this reflects the shift during recent years from a classical to a technological concentration in premedical education.

Nevertheless, I asked a crucial question in Dallas. Let me explain. I am a Southerner, born and reared in the Bible Belt at a time when North Carolina was a very segregated society. But I have had the good fortune to travel widely, particularly during WW II as a soldier and between 1965-75 when I was active in the international population movement. I have seen many cultures and religions and have observed that theological beliefs lead to ethical outcomes that are widely variant. Cultures exist which either condone or condemn the same acts, e.g., homicide, contraception, abortion and infanticide. I saw a TV feature on family planning in mainland China recently which made me wonder whether infanticide involving babies who are abnormal at birth may not become NORMATIVE there. Their new

policy of only one child per couple puts enormous pressure on parents for perfect babies. If practiced, selective infanticide would reduce the frequency of certain congenital defects, and might result in a marked change in the sex ratio of the next generation in the direction of a favored sex. Chinese have historically preferred males. Furthermore, the elimination of the children who are obviously abnormal at birth would reduce the frequency of many congenital anomalies and be a powerful selective force acting to reduce the frequency of the genes responsible for autosomal dominant traits. There would be little change in the frequency of recessive genes, but the frequency of recessive traits would probably decrease because of a reduction in in-breeding. There would be little effect on traits that do not become manifest until later in life, high intellect for example. Whatever its consequences, the one child policy is an obvious solution to the dilemma that faces the Chinese because of their enormous population, and this is the context in which we must now do our thinking. We must try to re-think our positions on various ethical questions before we are forced like the Chinese to consider tremendous changes.

My first attempt to establish a personal position on medical ethics was simple and practical, and I suspect that most physicians have done something similar. I fell back on the ethical values I picked up during childhood, e.g., the Golden Rule and the story of the Good Samaritan, modified in sundry utilitarian ways. I do not pretend that I have found a much better philosophy in recent years, even though I have continued to struggle with the philosophical contradictions and inconsistencies that have bothered me since childhood. What I mean by the latter comment is that I decided to become a physician largely because it seemed to a teenager to be a solution to the puzzling problem of reconciling ethical values and life in the real world. I was unable to see how to simultaneously practice the Golden Rule and succeed in business.

It has been a long time since the simple statements of the Hippocratic oath have been very useful to medical practitioners or to thinkers about medical ethics. Medical ethical values constantly change because the technology and content of medicine are rapidly evolving. Technological change has been so fast recently that institutes, specialty journals, and national meetings have sprung up which deal solely with problems of medical ethics. Let me give three examples.

1) The Hastings Center is a voluntary agency located north of New York City which was organized by a former Catholic theologian. It operates on contributions and publishes an excellent journal. I have been a subscriber since 1973, and I find articles of interest in almost every issue.

* My interaction with the AHA was not a complete disaster. I converted my presentation into a paper later published in *Perspectives in Biology and Medicine* with the title "Ethical and social issues posed by genetic studies of cardiovascular disease" (20:260, 1977).

From the Department of Pathology, The University of North Carolina, Chapel Hill 27514.

The Center has been particularly concerned recently with the abortion issue, the application of genetic engineering to humans, the problems of the homosexual, the AIDS syndrome, how to manage badly disabled infants, and the elderly.

2) The Kennedy family has endowed an institute at Georgetown University devoted to studies of "bioethics." The institute, now headed by Dr. Edmund Pellegrino, has published an encyclopedia which contains papers on almost every conceivable topic in biology and medicine which might cause ethical problems.¹ This approach to the subject has been analyzed and cogently criticized by two well-known medical anthropologists, Renee Fox and Judith Swazey.²

3) Recently I received a flyer advertising a national conference whose purpose was to implement in community hospitals the findings of the President's Commission For The Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. I seem to be invited to 4 or 5 similar meetings each year. The speakers are lawyers, philosophers, nurses, social workers and physicians. The keynote speech at this one was to be given by Morris Abram, a lawyer and former President of Brandeis University. He was also Chairman of the now defunct Commission. His topic, *mirabile dictu*, was "Ethics in a Pluralistic Society"! I am happy to see that he is attacking the problem which has interested me. I look forward to whatever answers he has found.*

Hippocrates's implied injunction relative to medical experimentation was very simple. He said, "Do no harm." Certainly no physician or ethical investigator wants to do harm. On the other hand, this was not a very useful guide, as physicians discovered well before our own day, and technological progress has made the problem considerably more difficult.

At the beginning of the century, American medicine, led by Dr. Benjamin Rush of Philadelphia, had developed what has been called a system of "heroic medical care." It was tough upper lip all the way! Surgeons operated without anesthesia, and it was regarded as character building to undergo an amputation without having the pain deadened. This type of medical care was being widely practiced when general anesthesia was discovered in mid-century. The use of inhalation anesthesia in its various forms and pain deadening drugs of the opium type were adopted very rapidly. The initial debate concerned the character destruction that might result from the use of pain deadening agents. Then it was discovered that ether and chloroform were toxic to the liver, and opiates could be addictive. The debate shifted to how to calculate the costs vs. the benefits of the abolition of pain. This is essentially where we are today. Every new therapeutic agent, operation, or device is carefully examined from the point of view of usefulness, as to whether it is better than another therapy, and whether its side effects are worse than the condition being treated.

* Mr. Abram has been in the news lately in another context, having just been appointed chairman of the Commission on Civil Rights by President Reagan. You may have seen him on television locking horns with Dr. Mary Berry, a member of the recent Carter administration. One cannot help admiring Mr. Abram. I don't know whether to admire him more for tackling the issue of ethics in a pluralistic society or for taking on the formidable Dr. Berry.

Let us look more closely at the classical definition of the physician's role: restoring health, preserving life, and combating suffering. What is he to do when the three are in conflict? What is to be done when relief of pain requires the giving of a dangerous drug; or when curing a disease requires radical and disfiguring surgery; or when life can be preserved only at a high cost in pain and anguish? Should a terminal cancer patient be given a potentially lethal dose of painkillers? Should heroic therapy be used to achieve a brief prolongation of life during a terminal illness? Everyone agrees that the duty to relieve suffering overrides the duty to prolong life. But is there a particular type of assessment that might provide answers to such ethical dilemmas?

This predicament led Joseph Fletcher and others to propose "situational ethics" as the solution about two decades ago. Situational ethics is the term that stands for the idea that each instance should be ethically judged on its own merits. This sounds like an excellent way to solve ethical problems. The difficulty is that it is extremely time consuming. It means that a physician can deal with only a few patients, because much of his time will be devoted to the systematic philosophical analysis that precedes the taking of action. In complex circumstances, the patient might expire before the doctor completes the analysis.*

What are the special ethical problems posed by human experimentation? To try to answer this, I shall turn to my ten year experience on NCMH's institutional review board (usually referred to nationally as an IRB), a group appointed by the Dean of Medicine and which actually bears the title: "Committee on Protection of the Rights of Human Subjects." I shall describe some aspects of the problems I observed and how we reacted. What we actually did was practice ethical calculus.

The committee consists of 14 to 20 persons, depending upon weather. It is widely representative of the medical center, and it includes 4 lay representatives from the community. A rotating cadre of students has been added recently. It meets monthly, and there are usually 10-20 items to be considered. It faces problems raised by the development of new drugs, new appliances, new diagnostic and surgical procedures, administration of novel types of radioisotopes, etc. I shall describe the evaluation of a new and untried drug from discovery until approval, because although this matter looks relatively straightforward, it is complex and controversial and raises all facets of our main question.

Before a new drug can be introduced into regular medical practice it must undergo an extensive screening procedure leading to approval by the Food and Drug Administration. The drug was probably synthesized in a chemical laboratory somewhere and has been found to have a therapeutic effect of some sort, probably by testing it on an animal. What must be understood is that every potential drug is also a potential poison. After a therapeutic effect has been discovered, the toxic side effects are examined in experimental animals by the manufacturer or his delegate. Ethical problems arise early, because there are those who

* In recent years philosophers and/or theologians have been recruited to medical faculties, e.g., Joseph Fletcher at the University of Virginia and Larry Churchill at UNC. There is now an elective course in medical ethics at Chapel Hill.

doubt that animals should be used for these purposes. Yet there seem to be few ways to discover the therapeutic value of drugs except by observing their effects in animals. Notable exceptions are the drugs that are useful against bacteria and cancer. Their effectiveness can be partially evaluated in bacterial or cell cultures.* But how can we discover in cultures a drug that has an effect on consciousness or blood pressure? With important exceptions, there are few avenues other than animal testing that evaluate toxicity adequately. The exceptions are mutagenicity and carcinogenicity which can be tested for in cultures. But these are only two of the many toxic effects that concern us. Some drugs do not become toxic, for instance, until they have been transformed by exchange between the cells of the different organs within an animal. There is no way to establish cell cultures or sets of cell cultures, which simulate animals, even using computers! An intact animal whose metabolism is similar to man's provides the only entirely reliable test system. If non-human animal studies were to be abolished the development of new drugs would have to cease, unless we were willing to use humans in their stead. To believe that we should cease to make new drugs is an entirely respectable intellectual position. However, those who advocate continuing to develop new drugs, and also advocate abolition of toxicity studies in animals can profess this view ethically only under the following proviso: They must be willing to volunteer their own bodies.

When animal studies have shown that a drug is not too toxic, this must still be verified in humans. All new drugs must undergo what are called first and second phase human studies before they are approved by the FDA, since the metabolism of no other mammal is exactly like that of man.

In first phase human studies the proposed therapeutic dose of a drug must be shown to be essentially nontoxic in volunteer subjects. Many drugs that are not toxic in usual doses may be highly toxic in larger doses. Furthermore, a dose that is suitable for the average subject may constitute an overdose for subjects who are overly susceptible for genetic reasons. It is impossible to be absolutely certain that a drug is innocuous to everyone.

If the toxicity studies are successful, it is then necessary to study the effectiveness of the agent, phase two. Is it really better than a similar agent? If it is either clearly less toxic or clearly more effective, it will probably be widely adopted. At a teaching hospital, the members of the faculty are frequently involved in testing drugs for pharmaceutical companies, both in first and second phase studies. At almost every meeting, our local IRB considers one or more new drugs or new uses for older drugs.

In addition to new drugs, there are new appliances or procedures such as isotopic scanning, new forms of radiation therapy, cardiac catheterization, diagnosis of brain tumors by isotopes, use of nuclear magnetic resonance spectroscopy, etc. to be evaluated. Sometimes the requests come from members of the faculty who have developed appliances, but more often a manufacturer wants a faculty

member to test the utility of a new device. The IRB must be certain that application of the new tool or procedure does not endanger the subjects in any way or impair their rights. It also asks whether the expected benefits might be obtained in a simpler or cheaper fashion. The committee always makes an estimate of the risk versus the benefit. It tries to judge whether the gain to the patient outweighs the risk. This question must be settled before the new apparatus can be ethically put into use in the hospital.

Another type of problem arises when a new diagnostic procedure is suggested. Someone thinks or discovers that a new procedure may provide clearer evidence for or against the diagnosis of some disease. But the procedure itself is dangerously invasive or unpleasant. For example, prenatal diagnosis can be carried out by studying bits of the placenta of pregnant women utilizing the methods of recombinant DNA technology. The risk is that obtaining the tissue may lead to a miscarriage. The question comes down to an estimate of the ratio between the danger of using the procedure and the benefit that might accrue from its use.

Why are such problems presented to an institutional review board? Where do they come from? It seems to me that the proposals originate from about five sources.

1) Young, energetic and enthusiastic faculty members who put forward new ideas about improved diagnosis or therapy that need testing. If they are correct this outcome will lead to publication and the authors will enhance their reputations. Most of the proposals come from this group.

2) Pharmaceutical firms or foundations whose products must be reviewed by a reliable group, such as the staff of a university hospital. They recruit faculty members as agents and expect the institution to provide the subjects. This is not a type of research that often brings high acclaim to faculty members, but it is very useful to society.

3) Federal agencies in the area, particularly the Environmental Protection Agency and the National Institute of Environmental Health Sciences. The staffs are studying the effects of toxic substances on humans, and they often wish to define the effects of, say, lead or carbon monoxide on the function of the heart or lungs. They usually propose well-designed experiments involving volunteer subjects. Some of their employees are also faculty members, and some of the agencies have established special facilities on the campus.

4) "Cooperative Cancer Protocols." The doctors who specialize in treating cancer, the oncologists of our country, have banded together, by specialties, to test the efficacy of various combinations of drugs on the treatment of various types of cancer. Their proposals are formulated at a central location, and then farmed out to the institutions belonging to a consortium. Our institution belongs to several such consortia.

5) Graduate students. They wish to do thesis research on human subjects, the research project being a requirement for the graduate degree. Of course the work is carried out under the direction of a responsible faculty member.

The members of the local IRB have seen many examples of these different types of requests. In each case, the committee has judged the proposal by criteria established earlier as necessary for ethical experimentation on humans. I wish to emphasize that a physician who tried to avoid the

* The original cancer drugs were discovered by studying their effects on animals that had cancer. More recently cultures of cancer cells have been devised for screening potential cancer drugs. Everyone agrees that any test tube method that accomplishes the same task as animal studies should be adopted.

sometimes tedious IRB process would be disciplined. An investigator must provide suitable answers to the following questions:

Will the subjects truly be volunteers?

Will "informed consent" be obtained from these volunteers?

Is the study sufficiently well organized that a clear-cut answer can be obtained?

Is this the testing of a new procedure or merely the testing of a substitute for an already established and satisfactory procedure?

Will the results obtained be held in confidence?

Is the result, if obtained, sufficiently important to justify doing the experiment?

These are stringent questions and investigators are compelled to answer them. If answers are not forthcoming, or are not satisfactory, approval is withheld. Problems may arise in the following areas.

Volunteers

Many proposals are carried out on normal subjects, e.g., the Phase I drug toxicity proposals. The investigator usually advertises for and pays volunteers for compliance. Volunteers are plentiful in the Triangle area.*

It is more difficult to obtain volunteers when the subjects are patients. If the experimenter proposes to test the efficacy of a new agent against a condition that is not life-threatening, affected persons are often quite willing to cooperate. They are sometimes eager to test new agents for relatively benign conditions, such as acne, for which present agents are far from perfect. They may well benefit from participation in the experiment.

But finding volunteers is more difficult when the disease is life-threatening. When patients understand that they have apparently intractable cancer they may volunteer. But they are less willing to volunteer if the outcome is more hopeful, unless there is evidence suggesting that the new therapy may be better than present therapy. It would be unethical for a physician to attempt to force cooperation with the testing of a new treatment by suggesting or implying that the current therapy might be withheld otherwise. Knowledge of such an occurrence would bring down on an investigator the full wrath of the committee.

Informed Consent

Each experimenter must prepare a special consent form for his project. This is supposed to explain to the subject, in layman's language, all the risks and benefits. Then being informed, the subject gives or withholds consent.

The consent forms are very often poorly prepared. They tend to be badly written, full of jargon and technical terms, and hard even for committee members to understand. The committee returns more proposals to investigators because

of badly written consent forms than for any other reason. My feeling is that even when the consent forms look and sound good to committee members, they are often unintelligible to subjects. Many patients are of reduced physical or mental capacity, or are poorly literate. They often stand in awe of the investigator, tending to agree uncritically with his suggestions, and don't want to challenge him. He is their doctor! There is good empirical evidence that the degree of understanding by a subject is inversely related to the length of the consent form, and some of the forms are 2-3 single-spaced pages!

Informed consent is a special problem when the subjects are fetuses, infants, or the elderly. It is a real problem, for example, to be certain that one has obtained informed consent to study Alzheimer's disease (senile degeneration). How can anyone be certain that the patient has understood and that manipulation has not occurred?

Organization of the Project

It is usually easy for the committee to decide whether a proposal has been so organized that a clear answer can be obtained. When this is not the case, the proposal is returned to its originator. It is usually revised and returned, but a few are so poor that they never again see the light of day.

Improving an Older Therapy

Many proposals are not aimed at testing radically new therapies. Rather there is an attempt to obtain marginally better results from an accepted one. If acceptable by all other criteria, and there is no added risk, these proposals are usually approved.

Confidentiality

Many investigators propose to collect personal data on large numbers of subjects for statistical analysis. Our rule has been that the subject's name must be so coded that no possibly embarrassing information can fall into the wrong hands. This is particularly important when psychosocial information is being collected.

Importance of the Experiment

The committee is seldom unanimous about the importance of a suggested experiment. There is clearly a sort of "Heisenberg principle" operating, and it would seem that "importance," like beauty, lies in the eye of the beholder. But in the absence of strong objections, and all other criteria having been met satisfactorily, an experiment is usually approved on the ground that the committee is not infallible and could be wrong about its importance.

Conclusion

I found service on an IRB to be very interesting and informative. I learned what many of my colleagues were doing without expending much energy, and got to know a number of interesting younger people whom I would never have met otherwise. (This is, of course, the real justification for large committees.) I felt on a number of occasions that we had shielded subjects from unnecessary risks. In the main, however, the proposals were satisfactory and were approved. As sportswriters sometimes say about athletic programs, the review of human experimentation at NCMH

* Consideration of the ethics of experimentation on human subjects, volunteers and patients, is much more advanced in the USA than Europe and Japan. It is at present the subject of intense debate in both Britain and France.

now has tradition. The medical faculty know that the committee exists, know that it is critical, and know that it must be reckoned with. Badly prepared and/or inappropriate proposals are now very rare.

As for my own contribution, I decided early on to play the role of Hippocrates. I left detailed criticism of the consent forms to our lay members, and left detailed criticism of scientific validity to my better educated younger colleagues. I attempted merely to be certain that none of the proposals did any harm.

So what are the special ethical dilemmas of human experimentation? It is not that the issues differ in principle from ordinary issues of medical ethics. It is that the issues are so complex and the ramifications so obscure that it is sometimes impossible to unravel them in any sort of timely fashion. Yet the subjects, patients, cannot be set aside to await the ethical analysis. The technical questions and their ramifications are often beyond the comprehension of the lay members and even the scientists. Yet the IRB must

function as a "situational ethicist" functions, making ethical judgments about experiments on humans on a case-by-case basis. Sometimes I felt certain that the ethical analysis and the conclusion were correct. Other times I felt that the ethical situation was unanalyzable. Yet a decision had to be made. It was on these occasions that I reached for Occam's razor and cast my vote, based upon my calculation of the probability that harm would result. Thus we see that examining the ethics of human experimentation merely provides another venue for agonizing, existential decision-making. This is what physicians have always been expected to do and is why, when they are true to their principles, they are so highly regarded.

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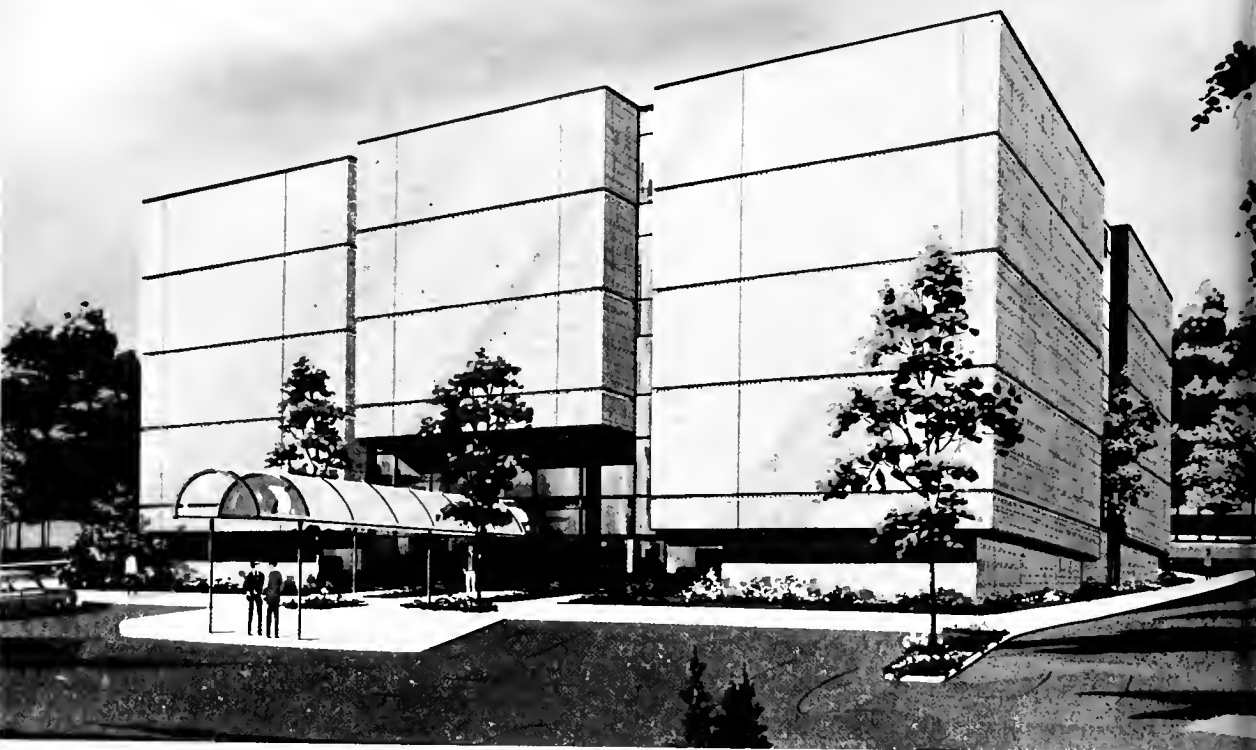
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Inaugural Address

Linda P. Nance

AS I stand before you today, I think of the many invested hours of preparation that have brought me to this point. The travel that has taken me to your counties and districts has left me with treasured friendships and I feel that I know about many of your opportunities. It is, therefore, with a great sense of pride and honor that I step forward to serve as your president.

There have been many women who have given outstanding leadership to the North Carolina Medical Society Auxiliary, a beautiful string of pearls. These women have brought us to the position of importance which we hold today. The eighties have seen great growth and change in the professional quality of what we offer in leadership training, opportunities for personal growth, and one-on-one contact between state officers and county members.

The world is in a state of change, and the Medical Auxiliary has attempted to keep up with these changes. We are not just a Women's Auxiliary now, we have male members, and women's roles are different. We are attempting to address these changes with programs that will develop one's potential. The National Auxiliary has developed the Professional Skills Program to document seminars, workshops, and educational participation which can be applied in the business world or in building self confidence. In this way we promote ourselves, our skills, and our organization.

As an organization we can effect positive change in our communities. There are many opportunities for us as medical families to make a difference. We can make citizens aware that there are ways to cut medical costs by changing the way they live. Fewer than 40% of North Carolinians BUCKLE UP when they drive; there were 2,700 lung cancer deaths in 1983; 13% of the adults in North Carolina lead a sedentary lifestyle; and North Carolina exceeds the national average in the incidence of high blood pressure, diabetes, arthritis, and strokes. Does it sound too simple to say that all of this could change if people stopped smoking, used seatbelts, got more exercise, ate nutritiously, and did not drink and drive?

This is where we as Auxilians can make a difference. I hope you will arm yourselves with the facts and educate the

members of your communities as to the ways in which they can improve the quality of their lives. Work with your county Medical Society to form a partnership to help promote a positive image for medicine.

Because at least 625,000 children in the United States are reported abused or neglected each year, the state's major focus for the 1984-1985 year will be Child Abuse and Neglect: Its Awareness and Prevention. Your Health Projects Chairmen will offer suggestions as to ways you might establish educational and support programs in your communities. The Legislation Chairman is keeping her finger on the pulse of the political scene for pending legislation pertaining to child abuse. Throughout the year she will keep you informed about this and other legislative issues facing medicine today. In September there will be workshops about automobile safety restraints, prenatal and post-natal care, and nutrition which will address the growing problem of anorexia nervosa and bulimia.

I have chosen as my theme, MAKE WAVES. I hope each of you here today will be inspired to return to your county to demonstrate our organization's concern with the public health of its citizens. Educate them about health-related issues with media spots, community programs, and by the example you set. From the programs that we will offer, you should find a project that will fit your Auxiliary, large or small. Continue to sponsor programs that are successful and still vital, but explore the needs in your community to see what you can do to expand your impact. You can make a difference!

Your officers are anxious to assist you in implementing programs, to help you meet your specific opportunities, or to be available when you need any advice. Please call on us.

Like the beautiful butterfly that emerges after the changes in its cycle of development, let us capitalize on what our predecessors have accomplished to make the mid eighties important years in our Auxiliary's history.

Shape Up For Life, MAKE WAVES in your communities. Let everyone with whom you come in contact know that you care about what happens to them. Make small waves or large ones when you implement programs and projects which you have found to be needed. By this time next year you can tell all Auxilians whether the song of the sea ends at the shore or in the hearts of those who listen to it

From 1922 Brookhaven Road, Wilmington 28403.



**You may think these physicians
are working alone.**

But they really have a team behind them.

These physicians spend most of their day working independently in a one-to-one doctor/patient relationship. And chances are that as a physician, you do too.

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Tasks such as keeping government regulations from interfering with your practice by representing your interests at local and national levels. And challenging regulatory measures that threaten you and your patients' interests by mounting legal campaigns to defend your rights — up to the Supreme Court if necessary.

Why do we believe that *teamwork* means so much to all physicians — even those who work "alone"?

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For more information, contact your state or county medical societies, or call the AMA collect at 312 751-6196. Or return the coupon below to your state or county medical society.

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- ☐ I am a member of my county and state societies; please send me information on joining the AMA.

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Bulletin Board

Continuing Medical Education

Please note: 1. The Continuing Medical Education Programs at Bowman Gray, Duke, East Carolina and UNC Schools of Medicine, Dorothea Dix, and Burroughs Wellcome Company are accredited by the American Medical Association. Therefore CME programs sponsored or cosponsored by these schools automatically qualify for AMA Category I credit toward the AMA's Physician Recognition Award, and for North Carolina Medical Society Category A credit. Where AAFP credit has been obtained, this also is indicated.

IN STATE

June 17-22

Health Promotion — Wellness Institute
Place: Raleigh
Fee: \$250
Credit: 30 hours
Info: NC Health Promotion, Wade AHEC, 3000 New Bern Avenue, Raleigh 27610. 919/755-8018

June 20

Suicide by Poisoning
Place: Sanford
Credit: 2 hours
Info: R. S. Cline, M.D., Central Carolina Hospital, 1135 Carthage St., Sandford 27330. 919/774-4100, ext. 340

June 22-23

35th Annual Meeting and Scientific Sessions
Place: Durham
Info: NC Heart Association, Chapel Hill 27514

July 9-14

26th Annual Postgraduate Course/Morehead Symposium
Place: Atlantic Beach
Credit: 25 hours
Info: C. Easterling, Box 3108 Duke Hospital, Durham. 27710. 919/684-6878

July 13-14

34th Annual Blue Ridge Institute
Place: Black Mountain
Info: C. Scott Venable, American Lung Association of NC, 916 West Morgan Street, Raleigh 27611. 919/832-8326

July 18

Hospital Nutrition Update
Place: Sanford
Credit: 2 hours
Info: R. S. Cline, M.D., Central Carolina Hospital, 1135 Carthage St., Sanford 27330, 919/774-4100, ext 394

July 19-21

Sixth Annual Mountain Meeting
Place: Asheville
Credit: 12 hours, Category I AMA
Fee: \$150
Info: Division of Continuing Education, Bowman Gray School of Medicine, Winston-Salem 27103

July 30-August 3

Diagnostic Imaging
Place: Atlantic Beach
Fee: \$400
Credit: 26 hours
Info: J. D. Wright, Box 3808, Duke Hospital, Durham 27710. 919/681-2711

August 4

Geriatric Education Day
Place: Raleigh
Credit: 4 hours
Info: NCAFP 919/781-6457

August 7

Malpractice Awareness — STAT
Place: Greensboro
Info: Wayne Parker. 919/828-9334

August 14

Malpractice Awareness — STAT
Place: Charlotte
Info: Wayne Parker. 919/828-9334

August 15

Electrolytes/Arterial Blood Gases/Fluid Balance
Place: Sanford
Credit: 2 hours
Info: R. S. Cline, M.D., Central Carolina Hospital, 1135 Carthage St, Sanford 27330. 919/774-4100, ext 394

August 21

Malpractice Awareness — STAT
Place: Goldsboro
Info: Wayne Parker. 919/828-9334

August 24, 26

Summer Urology Conference
Place: Winston-Salem
Info: Division of Continuing Education, Bowman Gray School of Medicine, Winston-Salem 27103

OUT OF STATE

June 18-July 1

The Cancer Patient: Surgical Treatment and Rehabilitation
Place: Cruise Benice, Yugoslavia, Greece, Turkey, Russia
Info: C. Easterling, Box 3306 Duke Hospital, Durham 27710. 919/684-6485

June 18-22

New Horizons in Radiologic Imaging
Place: Charleston, SC
Credit: 20 hours, AMA Category 1
Fee: \$350
Info: Division of Continuing Education, Bowman Gray School of Medicine, Winston-Salem 27103.

June 27-30

Dermatology for Non-Dermatologists
Place: Myrtle Beach, SC
Credit: 15.5 hours Category 1 AMA
Fee: \$350
Info: Dermatology, Box 2987 Duke Hospital, Durham 27710. 919/684-6728

July 2-7

Midsummer Family Practice Digest
Place: Myrtle Beach, SC
Credit: 30 hours
Info: NCAFP. 919/781-6467

July 26-28

6th Annual Pediatrics Primary Care Conference
Place: Virginia Beach, VA
Credit: 12 hours
Fee: \$275
Info: S. Rosner, Box 48 MCV Station, Richmond, VA 23298. 804/786-0494

July 30-August 3

12th Annual Beach Workshop

Place: Myrtle Beach, SC

Credit: 20 hours AMA Category I

Fee: \$225

Info: Division of Continuing Education, Bowman Gray School of Medicine, Winston-Salem 27103

August 12-17

Symposium on the Surgical Treatment of Cancer

Place: Orlando, FL

Credit: 20 hours Category I AMA

Info: C. Easterling, Box 3108 Duke Hospital, Durham 27710. 919/684-6878

New Members

Donald Campbell Whiteside, 7624 S.W. 56th Avenue, Gainesville, FL 32608

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BURKE

Stewart Andrews Deekens, Jr. (FP), 350 E. Parker Road, Morganton 28655

CALDWELL

Robert Michael Wood (ORS), 715 Wilmore Drive, Lenoir 28645

CARTERET

Terrence Lynn Goodman (IM), P.O. Box 166, Atlantic 28511

CRAVEN-PAMLICO-JONES

Mack Dana Jones (N), 721 Professional Drive, New Bern 28560

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Rueben Norman Rivers (IM), 1738 Metromedical Drive, Fayetteville 28304

DAVIDSON

Marc Fedder (IM), 208-D W. Center Street, P.O. Box 557, Lexington 27292

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Dennis Israelski (resident), 7-D Post Oak Road, Durham 27705

Elizabeth Carol Jones (student), 2302 W. Club Boulevard, Durham 27705

Eugene William Linfors (IM), Box 3381, Duke Medical Center, Durham 27710

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Sydney Scott Stapleton (resident), Box 3802, Duke Medical Center, Durham 27710

Walter David Watkins (AN), Box 3081, Duke Medical Center, Durham 27710

Daniel Edward Wertman, Jr. (R), Dept. of Radiology, Durham Co. General Hospital, Durham 27704

FORSYTH-STOKES-DAVIE

Paul Hudson Gulley (resident), 1823 Grace Street, Winston-Salem 27103

Walter Dean Henrichs (D), 250 Charlois Blvd., Winston-Salem 27103

Sara Thompson Jones (AN), 321 Banbury Road, Winston-Salem 27104

Barbara Ann Murphy (student), 1759 Hawthorne Road, Winston-Salem 27103

Eric William Schmidt (resident), 140 Dalewood Dr. #6, Winston-Salem 27104

Robert Barclay Williams (student), 450 Lockland Avenue, Winston-Salem 27103

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James Morrison Poole (PD), 3803 Computer Dr., Ste. 207, Raleigh 27609

Sabra Alderman Woodard (R), 1825 St. Mary's Street, Raleigh 27608

Letters to the Editor

Allergies

To the Editor:

On January 9, 1984 I saw an 18-year-old white woman whose complaint was swelling of the eyes and throat.

Her first encounter with this reaction was on August 20, 1983. Her boyfriend had been trimming walnut trees and then came to visit her. Fifteen minutes after exposure to the walnut sap on his body, her eyes began to itch and swell. They did not completely swell shut. Her symptoms lasted three to four hours.

Two days later he again visited her after trimming trees and again had the walnut sap on his arms and wrists. Fifteen minutes after he arrived, her eyes swelled completely shut, her face was puffy and she experienced difficulty in breathing. She described this as feeling like her throat was closing and a tightness in her chest. She was taken immediately to the emergency room where she was given an injection of epinephrine and 25 mg of benadryl. She was released after 1½ hours with benadryl to carry home. Her symptoms lasted three to four days.

Four months later, she came home from school and ate an apple. Thirty minutes later she ate an orange. Then ten minutes later she ate a tangerine and a peppermint patty. After 15 minutes her eyes again swelled completely shut and the same difficulty in breathing was experienced. She took 50 mg of benadryl but to no avail. She was taken again to the emergency room where she was started on an I.V. of Jelco and Dextrose. She was given an injection of epinephrine and an injection of benadryl 50 mg, along with an injection of Decadron. She was kept in the emergency room for 5 hours before being released. She was given benadryl 25 mg capsules and an Ana-Kit to be used if necessary.

The most interesting and most important fact about this history is that sap is a rosin and rosin cross reacts with balsam of peru. Balsam of peru can be found in the following: topical medications, cements, liquids in dentistry, Anusol suppositories, Rectocaine suppositories, Endacaine compound suppositories, Granulex, rectal Medicone suppositories and ointment, Wyanooids HC, Calmol 4, Melynor ointment, cosmetics, hair tonics, perfumes, flavoring industry, china painting, oil painting, and adhesive tape. Balsam of peru cross reacts with the following: benzoin, rosin, benzoic acid, benzyl alcohol, cinnamic acid, essential oils, orange peel, eugenol, cinnamon, and clove.

Such a patient should be especially cautious when preparing for dental work. She should be patch-tested before any dental work is performed; otherwise a severe reaction could occur.

Balsam of peru cross reacts in many foods such as orange peel, celery, cinnamon, and clove. This would explain her reaction after eating the orange and tangerine.

I gave the patient information on where rosin and balsam of peru are found and what cross reactions can occur. I started her on a food elimination program.

I also spoke with Dr. Alexander Fisher regarding this case. He suggested that I patch test to balsam of peru, along with a dime-size piece of orange peel (inside and outside). This should be left on 20 minutes, then removed and the patient watched for one hour. Dr. Fisher did say that it is possible to have an anaphylactoid reaction from absorption to contactants. Therefore I am holding off on the patch testing.

I advised her to continue carrying her Ana-Kit at all times. I scheduled a followup visit in three months.

Claude A. Frazier, M.D.
Doctor's Park
Asheville 28801

Lessons in Medical Care From Outside North Carolina

To the Editor:

I have just returned from a two-week trip to Israel (my first) and would like to share some impressions that were gained. The trip centered around two professional experiences and a multitude of personal ones, all of which helped me appreciate the depth of the dilemma posed by the Middle East and its problems.

A. The first professional task, and the main reason for my going, was to visit the Ben Gurion University School of Medicine in Beersheba to watch the evolution of the Primary Care Program in that school. In visiting this school and program, I was able to be with young Israeli professionals as they worked in an exciting young university, in an area of the country which represents "the frontier" and in a program exploring positive change. The reality of much military presence, the reminders of recent past wars and losses, the possibilities of future attacks (daily air-raid drills for the school kids) and the disruptive requirement of military duty (being called up for the reserves up to age 55) on hospital and clinical staffing was quite evident.

The current economic crisis, with all wages lagging behind the 190% per year inflation rate, and the disruption that economic disorganization and diminishing buying power brings were evident. The earning power of professionals in the Israeli system is severely limited (around \$600 per month for teachers and physicians) while the cost of living is about the same as in the United States. There is a real sense of disorganization on the economic scene, with no strong proposals receiving much publicity.

The drains on the economy from maintaining the Israeli Army in Lebanon and from the development of the West Bank area are recognized as major costs that could be removed. None the less, the forces which led to these drains remain, and seem to be psychologically dominant. The lack of feeling of direct involvement in solving these questions and opening up greater rewards for professionals is only a small part of the general frustrations of the physicians with whom I talked. The governmental system in Israel, which involves voting for a party (not a person who would have to answer to his electorate), adds to the feeling of impotence.

Most of the two weeks in Israel was spent in Beersheba in the Primary Care Unit of the Ben Gurion University School of Medicine. This unit, part of the Department of Community Medicine, is interested in developing viable and interesting careers in Primary Care for Internists, Pediatricians, and Family Physicians (and secondarily improving primary care for the people). This is the context of a Health Care System which traditionally has strictly divided preventive, maternal and child health, and mental health services (the responsibility of the Ministry of Health), primary care (delivered through community clinics developed and staffed by the Kaput Holim — the health arm of the Labor Union organization), and hospital care, delivered in hospitals operated by either the Kaput Holim, the University, or the Ministry of Health (or in some instances private organizations). This organizational scheme tends to fragment care concepts such as "total," "continuing," and/or "holistic," and tends to limit the scope and professional responsibility and the possibilities for growth of the professionals involved. Added to this are the accumulated layers of bureaucracy, policy, and administration leading to suppression of initiative in such a structure.

Ben Gurion University School of Medicine and its teaching hospital provide a potential answer to these problems, as the three groups involved (the University, Kaput Holim, and Ministry of Health) are interacting under an administrative agreement and structure that allows the Dean of the Medical School authority for change.

There are many differences in the needs of the populations served by Ben Gurion. The rapid growth of Beersheba and the development of the Negev Desert through the development of new kibbutz and moshav communities and the new towns and suburbs bring to light medical care needs engendered by the psychological stresses of resettlement, culture shock environmental factors, as well as the expected problems of neglected chronic illness. The population is generally younger. There seem to be less alcohol-related problems. The positive psychological force of community (national) purpose has, up until now, offset problems of unmet expectations.

There is a particular population subset that Ben Gurion is exploring ways of serving, namely the Arab/Bedouin population in the Negev. These people are, in one generation, changing from a nomadic, sheep-herding, tent-living life style to a monetary based, Arabic part of a Hebrew speaking Jewish country. The problems of this predictably wrenching transition are immense, but already improvement in measurable health outcomes (like infant mortality) has been achieved. From a social anthropology point of view, this is the population with the most rapidly changing needs, and represents a population group in Israel that perhaps can be brought into the main stream without the tensions extant in the other Arab groups in the country.

Medically, the University is attempting to "open up" the possibilities for a new professional style for primary physicians which will not only improve primary care, but make it a visible and sought after career opportunity.

At this time the "experiment" consists of placing recent graduate M.D.'s into a primary care clinic setting for 1-2 years before their formal residencies in internal medicine, pediatrics, or family medicine to explore the realities and to

have supervised, responsible experiences in ambulatory care. This is being done in the Yoachim community (which is a community that is under much stress as a "failed-failing" socioeconomic entity), and in clinics in Beersheba. These clinic experiences are being augmented by didactic exercises weekly in the University.

They also involve association with and supervision of undergraduate medical students, but so far have not received any qualification as credit in any residency program. The value of a primary care experience in sharpening clinical skills was evident in the graduates of the program encountered in the hospital ward. Regular residents in Internal Medicine in the hospital, however, did not have access to or regular training in ambulatory care — either of previously hospitalized patients or of patients seeking primary care for medical conditions. It was also evident that the level of technology under the direct control of and easily accessible to those working in the primary care setting was limited. Hence, "ambulatory" care often, of necessity, became "hospital" care, and those responsible for the primary care did not carry the responsibility on into the hospital. I realize that the current system clearly separates these physician functions — but it leads to inefficiencies and a sense of professional isolation for those doing the ambulatory care.

This, in my mind, is the major improvement that can be made in the experience in training in primary care. If the continuum of medical care responsibility can be extended into the hospital and back out, the goals for the medical care rendered can be clarified.

The "experiment" and the goals behind it are to be commended, and the movement and development in the model have started the process of attracting young physicians to this style of medicine. Overriding these "internal" facts, however, are the external pressures on medicine and the rewards for being in the profession that may negate these good things. The "physicians' strike" last year really hurt the image of the profession (as judged by both medical students and faculty), and the means of rewards for physicians in the economic system — which is becoming unravelled — seems to discourage many of the young people. This can only be offset by pride and community within the profession.

B. The second professional opportunity came on visiting Jerusalem and being with Dr. Ted Tulchinsky in the Ministry of Health. He allowed me to become immersed in the health care needs of the Arabs and on the West Bank, and in efforts to meet those needs (as well as meet and talk with students and faculty in the School of Public Health at Hadassah). This was a most enlightening and intense experience, and it offered me an intense seminar in Arab-Jew relationships, the psychology (anguish and hatred) of an "occupied" people, and the evolution of a modern medical care system for the people of the West Bank. I visited the new (sparkling and beautiful!) clinic in East Jerusalem generated by Mayor Teddy Kollick which tries to cut across the preventative/therapeutic bureaucratic split in the health care services in Israel. It also, because of its ambience and convenience, is attracting Jewish patients for its services — a first step in breaking the Arab-Jew segregation?

The visit to the Arab hospital in Bethlehem afforded

some dramatic experiences highlighting the problems of providing modern medical care in a bureaucratically segregated system that is trying to set economic priorities for health care goals. A young Arab (ex-medical student) patient, who was transferred into the general hospital from the mental hospital, died while we were making rounds. The physicians — trained in the biomedical model — formulated the medical problem and its solution in terms of technology not available to them. The administrative barriers to transferring this patient to the Hadassah Hospital I.C.U. (the patient was uninsured, the Beit Jallah Hospital had already "used" its 8 transfer slots for the month, etc.) were vividly displayed and highlighted many of the "delivery" problems for the West Bank people.

Since the 1967 War, there has been marked improvement in medical care, with improvement in all outcome measurements. Along with this has been gradual incorporation of the people (and physicians) into the system with almost 50% of West Bank Arabs having health insurance at this point. I was able to participate in a specialty clinic (Hematology/Oncology) at the Beit Jallah Hospital where Dr. Horne, a Jewish physician, brings his team of Arab fellow-residents and sees the patients in the area. This team holds clinics in the other hospital in the West Bank, and is another instance where medicine might break down the barriers between Arabs and Jews.

Unfortunately, the mind set of "occupied territory-enemy country" seems pervasive, and though many missionary types like Tulchinsky and Horne are working away, there are counter-forces that seem to overshadow them. I hope their efforts dominate.

In summary: this trip was a most instructive immersion into the health care system of training for Primary Care in Israel, as well as a look at Arab/Israeli tensions via a look at health care on its West Bank. Israel is an inspiring and wonderful country. I have faith that the historical and deeply rooted animosities can be overcome, and that the good things I saw in Israel can be spread throughout the Middle East.

James A. Bryan II, M.D.
Department of Medicine
Chapel Hill 27514

Disposing of Radioactive Waste

To the Editor:

I am writing to ask your assistance in notifying your readership about the American College of Nuclear Physicians (ACNP) Professional and Public Information Program and the important issues of Nuclear Medicine and related low-level nuclear waste disposal. The ACNP is striving to educate the non-nuclear medical community and referring physicians about these topics by providing members of our Speakers Bureau — without charge — for major meetings of all medical specialty societies, state and major county medical societies, and other health-related organizations.

Since almost all medical research involves radioisotope techniques, these topics have a direct impact on all practicing physicians. The proper understanding of Nuclear Medicine and the low-level waste issue is critical to the continuity of clinical practice and to the future of medicine. Despite

its many benefits, the average patient erroneously fears Nuclear Medicine because it involves the use of small amounts of radioactive materials.

The low-level radioactive waste generated by Nuclear Medicine and biomedical research must be transported and disposed of at licensed disposal sites. Currently there is a critical shortage of these facilities. According to the Federal Low-Level Radioactive Waste Policy Act of 1980, each state must pass legislation either to enter into a regional compact for disposal or to establish its own facility by January 1986 or the generation of waste within its boundaries must stop.

Although physicians and patients want the benefits of advanced medical technology many oppose the concept of disposal sites due to their fear of radiation. If, however, the waste management problems are not solved, the practice of Nuclear Medicine and much basic medical research will be in jeopardy. Your prime readership is in a position to disseminate accurate information and address misconceptions when questioned by patients or the public about these issues.

If you are interested in writing about these issues or publicizing our Speakers Bureau, please contact me at (202) 857-1191. I will be happy to make arrangements for you to interview one of our speakers or provide you with additional information.

Barbara C. Teele
1101 Connecticut Avenue, N.W.
Washington, D.C. 20036

Two Letters to Walter Kempner

Dear Dr. Kempner:

I just want you to know how much I enjoyed your nice article, *Hands Across The Sea: The Durham Connection to Germany* [NCMJ 45:25-26, 1984].

I am sure that you now look back on the years 1927-1928 spent with Dr. Warburg as among the most interesting and most satisfying of all of your experiences during your brilliant career.

Kenneth Pickrell, M.D.
2609 North Duke Street
Durham 27704

Dear Dr. Kempner:

Bob Gutman just sent me a copy of your article, *Hands Across The Sea: The Durham Connection to Germany*. I thought you might like to hear my story about that.

During my residency in internal medicine at the II. Medizinische Klinik in Munich I also was working on my Dr. thesis with Prof. Zinnitz. It was a *Literaturarbeit* about which I am not exactly proud, and which dealt with allergic aspects of renal disease. Zinnitz was very well acquainted with your rice diet (1950) which he used on his patients and which he told us about a lot. I also remember that he told us to never use it on outpatients because he felt, well, he knew that the folks would not adhere to it. Nevertheless, this was the first time I heard about Duke and, indeed, was really the reason why it was Duke which was first on my list when I was looking around for an academic career after finishing my residence in Pathology.

If I had retained interest in the kidneys I might have

wound up in your corner, perhaps. Actually, several times I meant to ask you if I could go on rounds with you. But, ah, for all those distractions that keep crowding one's life.

Joachim R. Sommer, M.D.
Department of Pathology
Durham 27710

Sulfites in Medicines

To the Editor:

Most physicians are aware that the ingestion of foods containing added sulfites can cause allergic-like reactions in susceptible patients. The anti-oxidant properties of sulfites (sulfur dioxide, sodium sulfite, sodium and potassium bisulfite, and sodium and potassium metabisulfite) are used to preserve the quality and appearance of the food. As of July 1, 1983 at least 90 reactions had been reported to the Food and Drug Administration (including one fatality) in both asthmatics and nonasthmatic patients with no known allergies.¹ The symptoms of reactions to sulfites can include generalized pruritis, flushing, hives, shortness of breath, wheezing, and fainting. The signs of the reaction include erythema, urticaria, angioedema, laryngeal stridor, asthma, cyanosis, hypotension, and even respiratory arrest.

Although most reactions occurred after the ingestion of foods, prescription medications may also contain sulfiting agents to prevent oxidation.^{1, 2} Unfortunately, pharmaceutical products containing sulfiting agents are not presently required to list such additives on the product label, package insert or generally available descriptions of the product, since they are currently classified as GRAS (Generally Regarded as Safe) by the Food and Drug Administration.

Physicians should be aware that a review of generally available information about pharmaceutical products will not reliably identify safe formulations for use in sulfite-sensitive patients. A table of medications known to contain sulfites is enclosed. The Food and Drug Administration is currently considering implementing regulations that would require the identification of added preservatives on the product label.¹ In the absence of this regulatory change, reliable information about medications safe in sulfite-sensitive patients can be obtained only by contacting the manufacturer.

This recent experience with sulfite compounds provides an invaluable lesson about instances of presumed drug allergy. It seems likely that many allergic reactions to drugs, attributed to the principal component of the medication, may have been caused by seemingly safe additives. The possibility exists that patients currently considered allergic to certain drugs could safely use the active component of the medication. This possibility is an appropriate consideration in those patients who are known sulfite reactors.

Other additives and stabilizing agents are likely to be developed for use in medications in the future. Our recent experience suggests that current methods for the scientific assessment of the safety of these compounds are not adequate. Indeed, there is no evidence that any scientific method of study and review will provide complete assurance that a drug or additive compound will not cause an

idiosyncratic adverse reaction in a small, possibly genetically susceptible part of our patient population. Physicians should consider this possibility in patients who develop an adverse reaction to a medication. The active drug should not be identified as the cause of the reaction without a review of the possible role of additives.

A clear need exists for a concise statement of all the components used in pharmaceutical preparations on the product label or package insert.

Richard H. Drew, R.Ph.
C. Edward Buckley, III, M.D.
Duke University Medical Center
Durham 27710

References

1. Anon. Sulfites in foods and drugs. FDA Drug Bulletin 1983. 13:11-12
2. Akers MJ: Antioxidants in pharmaceutical products. J. Parenteral Sci Tech 1982. 36:222-228.

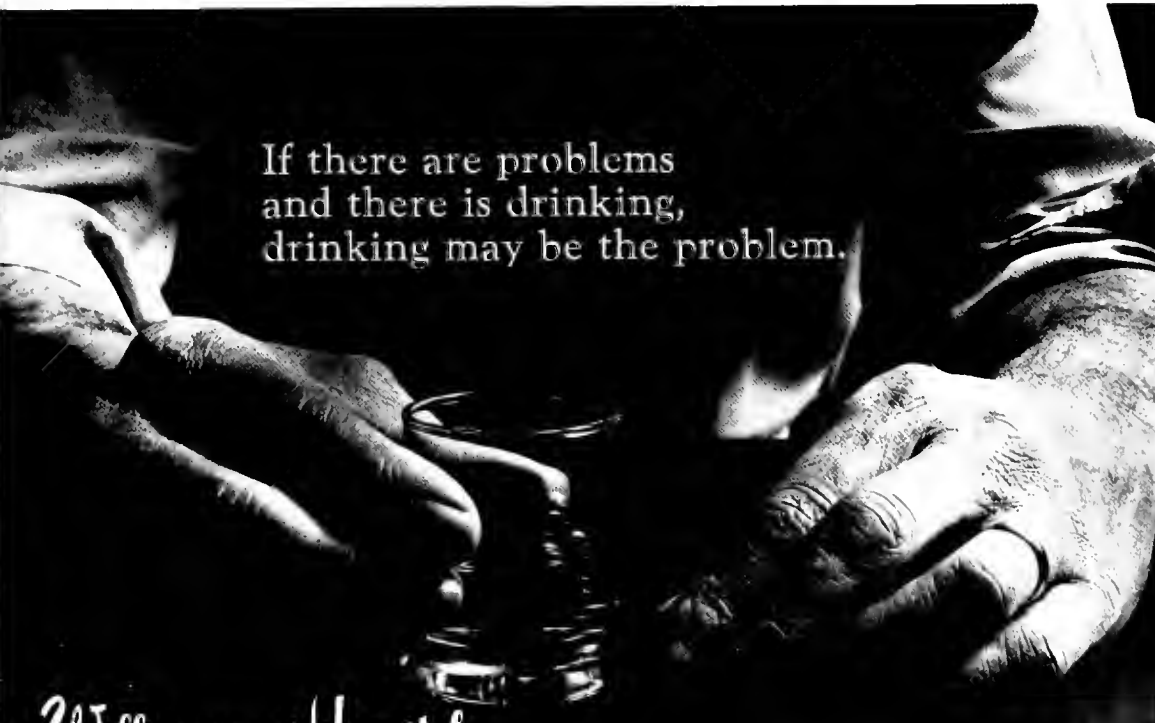
A Partial List of Sulfite-Containing Drugs*

Amikacin
Amino acid solutions w/electrolytes
Amino acid solutions without electrolytes
Angio-conray
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Ampicillin Resistant
Haemophilus influenzae

H. influenzae

S. pneumoniae

Brief Summary Consult the package literature for prescribing information

Indications and Usage Cefaclor* (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Lower respiratory infections including pneumonia caused by *Streptococcus pneumoniae* (Diplococcus pneumoniae), *Haemophilus influenzae*, and *S. pyogenes* (group A beta-hemolytic streptococci). Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Cefaclor.

Contraindication Cefaclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings IN PENICILLIN SENSITIVE PATIENTS: CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGICITY OF THE PENICILLINS AND THE CEPHALOSPORINS AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS INCLUDING ANAPHYLAXIS TO BOTH DRUG CLASSES.

Antibiotics including Cefaclor should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics including macrolides, semisynthetic penicillins, and cephalosporins; therefore it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life threatening.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate antibiotic therapy, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the drug has been discontinued or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be ruled out.

Precautions General Precautions—If an allergic reaction to Cefaclor occurs, the drug should be discontinued, and if necessary the patient should be treated with appropriate agents (e.g., pressor amines, antihistamines, or corticosteroids).

Prolonged use of Cefaclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive Direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antibody tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

Cefaclor should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

As a result of administration of Cefaclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinistest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly).

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Usage in Pregnancy—Pregnancy Category B—Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Cefaclor. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers—Small amounts of Cefaclor have been detected in mother's milk following administration of single 500-mg doses. Average levels were: 18, 0.20, 0.21, and 0.16 mcg/ml at two, three, four, and five hours, respectively. Trace amounts were detected at one

Some ampicillin-resistant strains of *Haemophilus influenzae*—a recognized complication of bacterial bronchitis*—are sensitive to treatment with Cefaclor.¹⁻⁶

In clinical trials, patients with bacterial bronchitis due to susceptible strains of *Streptococcus pneumoniae*, *H. influenzae*, *S. pyogenes* (group A beta-hemolytic streptococci), or multiple organisms achieved a satisfactory clinical response with Cefaclor.⁷

hour. The effect on nursing infants is not known. Caution should be exercised when Cefaclor* (cefaclor, Lilly) is administered to a nursing woman.

Usage in Children—Safety and effectiveness of this product for use in infants less than one month of age have not been established.

Adverse Reactions Adverse effects considered related to therapy with Cefaclor are uncommon and are listed below.

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70).

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely.

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100), pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis, arthralgia, and frequently, fever) have been reported. These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Cefaclor. Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.

Cases of anaphylaxis have been reported; half of which have occurred in patients with a history of penicillin allergy. Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain—Transient abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic—Slight elevations of SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematologic—Transient fluctuations in leukocyte count predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200).

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*Many authorities attribute acute infectious exacerbation of chronic bronchitis to either *S. pneumoniae* or *H. influenzae*.

Note: Cefaclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections including the prophylaxis of rheumatic fever. See prescribing information.

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Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. An additive effect may occur if alcohol is consumed the day following use for nighttime sedation. This potential may exist for several days following discontinuation. Caution against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Potential impairment of performance of such activities may occur the day following ingestion. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, abrupt discontinuation should be avoided with gradual tapering of dosage for those patients on medication for a prolonged period of time. Use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in severely depressed patients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, light-headedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase; and paradoxical reactions, e.g., excitement, stimulation and hyperactivity.

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